

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
12 June 2003 (12.06.2003)

PCT

(10) International Publication Number
WO 03/048163 A1

(51) International Patent Classification⁷: C07D 487/04,
A61K 31/505, A61P 25/00

RO, RU, SC, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UZ, VC, VN, YU, ZA, ZM.

(21) International Application Number: PCT/US02/37915

(22) International Filing Date:
26 November 2002 (26.11.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/334,385 30 November 2001 (30.11.2001) US

(71) Applicant: SCHERING CORPORATION [US/US];
2000 Galloping Hill Road, Kenilworth, NJ 07033-0530
(US).

(72) Inventors: NEUSTADT, Bernard, R.; 24 Brook Place,
West Orange, NJ 07052 (US). LIU, Hong; 15 First Street,
Apartment 6-D, Hackensack, NJ 07601 (US).

(74) Agent: MAGATTI, Anita, W.; Schering-Plough Corpora-
tion, Patent Department-K-6-1 1990, 2000 Galloping Hill
Road, Kenilworth, NJ 07033-0530 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ,
DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU,
ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV,
MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PH, PL, PT,

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK,
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted
a patent (Rule 4.17(ii)) for the following designations AE,
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,
CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB,
GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK,
LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ,
PH, PL, PT, RO, RU, SC, SE, SG, SI, SK, SL, TJ, TM, TN,
TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM, ARIPO patent
(GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR),
OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
ML, MR, NE, SN, TD, TG)
- as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii)) for all designations

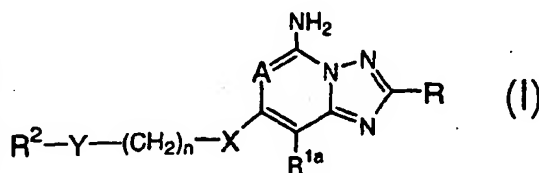
Published:

- with international search report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

WO 03/048163 A1

(54) Title: [1,2,4]-TRIAZOLE BICYCLIC ADENOSINE A_{2A} RECEPTOR ANTAGONISTS



(57) Abstract: Compounds having structural formula
(I) wherein: n is 0, 1, 2 or 3; A is C(R¹) or N; R¹ and
R^{1a} are H, (C₁-C₆)-alkyl, halo, CN or -CF₃; X is -C(O)-,
-O-, -SO₂-, or optionally substituted methylene, imino,
arylene or heteroaryldiyl; Y is -O-, -SO₂-, or optionally
substituted arylene, heteroaryldiyl, or nitrogen-containing
heterocycloalkyl, or with certain provisos, a bond; R is
optionally substituted aryl or heteroaryl; and R² is optionally

substituted aryl, heteroaryl, arylalkyl or heteroarylalkyl; or R²-Y is a fused piperidinyll, substituted piperazinyl or substituted
piperidinyll; their use in the treatment of Parkinson's disease, alone or in combination with other agents for treating Parkinson's
disease, pharmaceutical compositions comprising them and kits comprising the components of the combinations.

5

10

[1,2,4]-TRIAZOLE BICYCLIC ADENOSINE A_{2a} RECEPTOR ANTAGONISTS

BACKGROUND

The present invention relates to substituted [1,2,4]-triazole bicyclic adenosine
15 A_{2a} receptor antagonists, the use of said compounds in the treatment of central nervous system diseases, in particular Parkinson's disease, and to pharmaceutical compositions comprising said compounds.

Adenosine is known to be an endogenous modulator of a number of physiological functions. At the cardiovascular system level, adenosine is a strong
20 vasodilator and a cardiac depressor. On the central nervous system, adenosine induces sedative, anxiolytic and antiepileptic effects. On the respiratory system, adenosine induces bronchoconstriction. At the kidney level, it exerts a biphasic action, inducing vasoconstriction at low concentrations and vasodilation at high doses. Adenosine acts as a lipolysis inhibitor on fat cells and as an antiaggregant on
25 platelets.

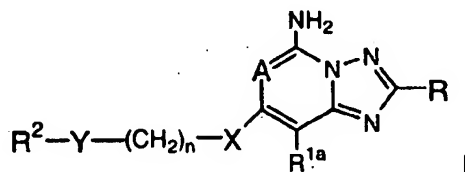
Adenosine action is mediated by the interaction with different membrane specific receptors which belong to the family of receptors coupled with G proteins. Biochemical and pharmacological studies, together with advances in molecular biology, have allowed the identification of at least four subtypes of adenosine
30 receptors: A₁, A_{2a}, A_{2b} and A₃. A₁ and A₃ are high-affinity, inhibiting the activity of the enzyme adenylate cyclase, and A_{2a} and A_{2b} are low-affinity, stimulating the activity of the same enzyme. Analogs of adenosine able to interact as antagonists with the A₁, A_{2a}, A_{2b} and A₃ receptors have also been identified.

Selective antagonists for the A_{2a} receptor are of pharmacological interest because of their reduced level of side effects. In the central nervous system, A_{2a} antagonists can have antidepressant properties and stimulate cognitive functions. Moreover, data has shown that A_{2a} receptors are present in high density in the basal ganglia, known to be important in the control of movement. Hence, A_{2a} antagonists can improve motor impairment due to neurodegenerative diseases such as Parkinson's disease, senile dementia as in Alzheimer's disease, and psychoses of organic origin.

Some xanthine-related compounds have been found to be A_1 receptor selective antagonists, and xanthine and non-xanthine compounds have been found to have high A_{2a} affinity with varying degrees of A_{2a} vs. A_1 selectivity. Certain imidazo- and pyrazolo-substituted triazolo-pyrimidine adenosine A_{2a} receptor antagonists have been disclosed previously, for example in WO 95/01356; WO 97/05138; and WO 98/52568. Certain pyrazolo-substituted triazolo-pyrimidine adenosine A_{2a} receptor antagonists are disclosed in US 09/207,143, filed May 24, 2001. Certain imidazo-substituted triazolo-pyrimidine adenosine A_{2a} receptor antagonists are disclosed in US Provisional Application 60/329,567, filed October 15, 2001. US 5,565,460 discloses certain triazolo-triazines as antidepressants; EP 0976753 and WO 99/43678 disclose certain triazolo-pyrimidines as adenosine A_{2a} receptor antagonists; and WO 01/17999 discloses certain triazolo pyridines as adenosine A_{2a} receptor antagonists.

SUMMARY OF THE INVENTION

The present invention relates to a compound represented by the structural formula I



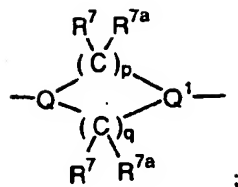
or a pharmaceutically acceptable salt thereof, wherein:

A is C(R¹) or N;

R¹ and R^{1a} are independently selected from the group consisting of H, (C₁-C₆)-alkyl, halo, CN and -CF₃;

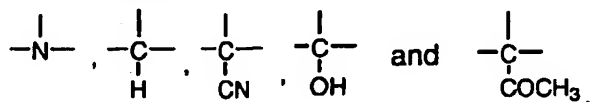
Y is -O-, -S-, -SO-, -SO₂-, R⁵-heteroaryldiyl, R⁵-arylène or

- 3 -



p and q are independently 2-3;

Q and Q' are independently selected from the group consisting of

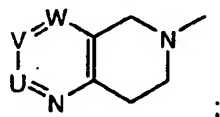


5 provided that at least one of Q and Q' is $\begin{array}{c} | \\ -N- \\ | \end{array}$;

R is R⁵-aryl, R⁵-heteroaryl, R⁶-(C₂-C₆)alkenyl or R⁶-(C₂-C₆)alkynyl;

R² is R⁵-aryl, R⁵-heteroaryl, R⁵-aryl(C₁-C₆)alkyl or R⁵-heteroaryl(C₁-C₆)alkyl;

or R²-Y is



10 U, V, and W are independently selected from the group consisting of N and CR¹, provided that at least one of U, V and W is CR¹;

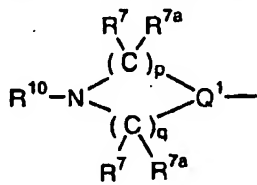
n is 1, 2 or 3; and

(a) A is C(R¹) and X is -C(R³)(R^{3a})-, -C(O)-, -O-, -S-, -SO-, -SO₂-,

R⁴-arylene, R⁴-heteroaryldiyl, or -N(R⁹)-; or A is C(R¹), Y is a bond, and X is

15 -C(R³)(R^{3a})-, -C(O)-, -O-, -S-, -SO-, -SO₂-, R⁴-arylene, -N(R⁹)- or R⁴-heteroaryldiyl, provided that when X is -N(R⁹)- or R⁴-heteroaryldiyl, R² is not phenyl or phenyl-(C₁-C₆)alkyl; or

(b) A is N, X is -N(R⁹)-, Y is R⁵-arylene and R² is



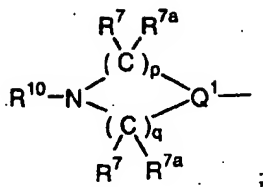
20 or n is 2 or 3; and

(c) A is N and X is -C(R³)(R^{3a})-, -C(O)-, -O-, -S-, -SO-, -SO₂-, -N(R⁹)-,

R⁴-arylene or R⁴-heteroaryldiyl; or A is N, Y is a bond and X is -C(O)-, -N(R⁹)-,

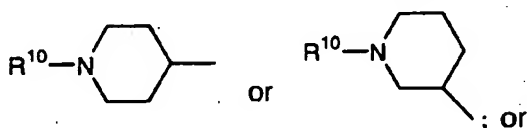
R⁴-arylene or R⁴-heteroaryldiyl; or A is N, Y is -N(R^{9a})-, -C(O)N(R^{9a})- or

$-\text{O}-(\text{CH}_2)_2-\text{N}(\text{R}^{9a})-$, and X is $-\text{N}(\text{R}^9)-$; or A is N, X is $-\text{N}(\text{R}^9)-$, and Y and R^2 together are

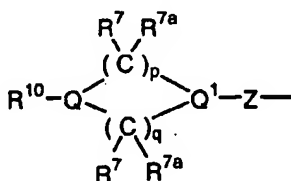


or n is 0; and

- 5 (d) A is N, Y is a bond, X is $-\text{N}(\text{R}^9)-$, and R^2 is



- (e) A is N, X is $-\text{N}(\text{R}^9)-$ and Y and R^2 together are



wherein Z is $-\text{C}(\text{O})-\text{CH}_2-$, $-\text{C}(\text{O})-\text{CH}(\text{C}_1-\text{C}_6 \text{ alkyl})-$, $-\text{CH}_2-\text{CH}(\text{C}_1-\text{C}_6 \text{ alkyl})-$,
 10 or $-\text{CH}(\text{C}_1-\text{C}_6 \text{ alkyl})-\text{CH}_2-$;

R^3 and R^{3a} are independently selected from the group consisting of H, $-\text{OH}$, C_1-C_6 alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl and di(C_1-C_6)alkylamino(C_1-C_6)alkyl;

- 15 R^4 is 1-3 substituents selected from the group consisting of H, (C_1-C_6)alkyl, $-\text{OH}$, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkoxy, halo, $-\text{CF}_3$, and $-\text{CN}$;

- R^5 is 1-3 substituents independently selected from the group consisting of H, (C_1-C_6)alkyl, $-\text{OH}$, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkoxy, halo, $-\text{CF}_3$, $-\text{CN}$, $-\text{NH}_2$, (C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl, (C_1-C_6)alkanoylamino, (C_1-C_6)alkanesulfonylamino, (C_1-C_6)alkylthio, (C_1-C_6)alkylthio(C_1-C_6)alkyl,
 20 $\text{R}^6-(\text{C}_2-\text{C}_6)$ alkenyl, $\text{R}^6-(\text{C}_2-\text{C}_6)$ alkynyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy- $\text{C}(\text{O})$ -amino, or heterocycloalkyl(C_1-C_6)alkyl;

R^6 is 1 to 3 substituents independently selected from the group consisting of H, $-\text{OH}$, (C_1-C_6)alkoxy and halo;

R^7 and R^{7a} are independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, R^8 -aryl and R^8 -heteroaryl, or an R^7 and an R^{7a} substituent on the same carbon can form =O;

R^8 is 1 to 3 substituents independently selected from H, (C₁-C₆)alkyl, -OH, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo, -CF₃, and -CN;

R^9 and R^{9a} are independently selected from the group consisting of H, (C₁-C₆)alkyl, hydroxy(C₂-C₆)alkyl, (C₁-C₆)alkoxy(C₂-C₆)alkyl, amino(C₂-C₆)alkyl, (C₁-C₆)alkylamino(C₂-C₆)alkyl, di(C₁-C₆)alkylamino(C₂-C₆)alkyl, halo-(C₃-C₆)alkenyl, CF₃-(C₁-C₆)alkyl, (C₃-C₆)alkenyl, (C₃-C₆)cycloalkyl and (C₃-C₆)cycloalkyl-(C₁-C₆)alkyl; and

R^{10} is H, -C(O)-O-(C₁-C₆)alkyl, R^5 -aryl, -C(O)-(C₁-C₆)alkyl, -C(O)-(R^5 -aryl) or R^5 -aryl-(C₁-C₆)alkyl.

Another aspect of the invention is a pharmaceutical composition comprising a therapeutically effective amount of at least one compound of formula I in a pharmaceutically acceptable carrier.

Yet another aspect of the invention is a method of treating central nervous system diseases such as depression, cognitive diseases and neurodegenerative diseases such as Parkinson's disease, senile dementia or psychoses of organic origin, or stroke, comprising administering at least one compound of formula I to a mammal in need of such treatment. In particular, the invention is drawn to the method of treating Parkinson's disease comprising administering at least one compound of formula I to a mammal in need of such treatment.

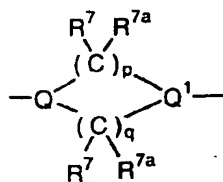
Still another aspect of the invention is a method of treating Parkinson's disease with a combination of at least one compound of formula I and one or more agents useful in the treatment of Parkinson's disease, for example dopamine; a dopaminergic agonist; an inhibitor of monoamine oxidase, type B (MAO-B); a DOPA decarboxylase inhibitor (DCI); or a catechol-O-methyltransferase (COMT) inhibitor. Also claimed is a pharmaceutical composition comprising at least one compound of formula I and one or more agents known to be useful in the treatment of Parkinson's in a pharmaceutically acceptable carrier. In the method comprising the administration of the combination of the invention, one or more compounds of formula I and one or more other anti-Parkinson's agents can be administered simultaneously or

sequentially in separate dosage forms. Therefore, also claimed is a kit comprising in separate containers in a single package pharmaceutical compositions for use in combination to treat Parkinson's disease wherein one container comprises a pharmaceutical composition comprising an effective amount of a compound of formula I in a pharmaceutically acceptable carrier, and wherein, in separate containers, one or more pharmaceutical compositions each comprise an effective amount of an agent useful in the treatment of Parkinson's disease in a pharmaceutically acceptable carrier.

10 DETAILED DESCRIPTION

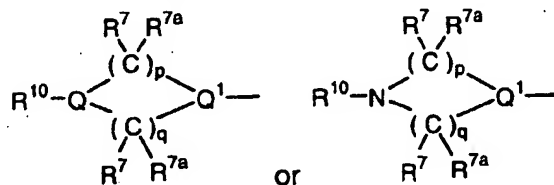
Referring to compounds of formula I above, preferred compounds of formula I are those wherein A is N. R is preferably furyl. R^{1a} is preferably hydrogen. Another group of preferred compounds is that wherein X is -O-, -S-, -N(R⁹)- or R⁴-arylene, with compounds wherein X is -N(R⁹)- being more preferred. R⁹ is preferably C₁-C₆ alkyl, with methyl and ethyl being most preferred.

Preferred definitions for Y are a bond or piperaziny (i.e., a group of the formula



wherein Q and Q' are each nitrogen, p and q are each 2, and each R⁷ and each R^{7a} is H). R² is preferably R⁵-aryl, more preferably R⁵-phenyl.

When Y and/or R² is



Q is preferably N, Q' is preferably N, p and q are each preferably 2, each R⁷ and R^{7a} is preferably hydrogen, and R¹⁰ is preferably -C(O)-O-(C₁-C₆)alkyl, -C(O)-(C₁-C₆)alkyl or -C(O)-(R⁵-aryl).

R⁵ is preferably 1 or 2 substituents selected from the group consisting of H, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)-alkoxy, halo and -CF₃. More preferred are H, methoxy, methoxyethoxy, fluoro and chloro.

R⁴ is preferably H, halo or (C₁-C₆)alkyl. R³ and R^{3a} are preferably independently selected from H and (C₁-C₆)alkyl. R^{9a} is preferably H or (C₁-C₆)alkyl. R⁶ is preferably hydrogen.

As used herein, the term alkyl includes saturated straight or branched carbon chains.

Halo means fluoro, chloro, bromo or iodo.

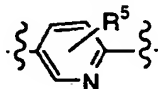
Alkenyl means a straight or branched hydrocarbon chain having at least one double bond. Similarly, alkynyl means a straight or branched hydrocarbon chain having at least one triple bond.

Aryl means a single aromatic carbocyclic ring or a bicyclic fused carbocyclic ring of 6 to 10 carbon atoms, for example phenyl or naphthyl.

Heteroaryl means a single ring heteroaromatic group of 5 to 6 atoms comprised of 2 to 5 carbon atoms and 1 to 3 heteroatoms independently selected from the group consisting of N, O and S, or a bicyclic heteroaromatic group of 5 to 10 atoms comprised of 1 to 9 carbon atoms and 1 to 3 heteroatoms independently selected from the group consisting of N, O and S, provided that the rings do not include adjacent oxygen and/or sulfur atoms. Examples of single-ring heteroaryl groups are pyridyl, oxazolyl, isoxazolyl, oxadiazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrazinyl, pyrimidyl, pyridazinyl and triazolyl. Examples of bicyclic heteroaryl groups are naphthyridyl (e.g., 1,5 or 1,7), imidazopyridyl, pyridopyrimidinyl and 7-azaindolyl. Also included in the definition of heteroaryl are benzofused heteroaryl groups comprising a heteroaryl ring as defined above fused at adjacent carbon atoms to a phenyl ring. Examples of benzofused heteroaryl groups are indolyl, quinolyl, isoquinolyl, phthalazinyl, benzothienyl (i.e., thionaphthenyl), benzimidazolyl, benzofuranyl, benzoxazolyl and benzofurazanyl. All positional isomers are contemplated, e.g., 2-pyridyl, 3-pyridyl and 4-pyridyl. N-oxides of the ring nitrogens for all heteroaryl groups are also included. R⁴- and R⁵-substituted heteroaryl refers to such groups wherein substitutable ring carbon atoms have a substituent as defined above.

Heteroaryldiyl means a heteroaryl ring bonded to two different groups. For example, in the context of this invention, when Y is R⁵-heteroaryldiyl, one ring member is attached to the group -(CH₂)_n-, and another ring member is attached to

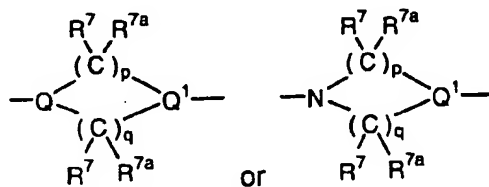
variable R^2 ; the R^5 substituents are attached to one or more of the remaining ring carbons. As an example, a pyridinediyl ring is shown:



Similarly, arylene means a divalent aryl ring, that is, an aryl ring bonded to two different groups, e.g., phenylene.

Heterocycloalkyl means a 3 to 6-membered saturated ring comprised of 2 to 5 carbon atoms and 1 or 2 heteroatoms selected from the group consisting of N, S and O, provided that two heteroatoms are not adjacent to each other. Typical heterocycloalkyl rings are piperidiny, piperaziny, morpholinyl, azetidiny, pyrrolidinyl, tetrahydrothienyl, tetrahydrofuranyl, tetrahydropyranyl and thiomorpholinyl.

When Y and/or R^2 comprise



each R^7 and R^{7a} substituent is independently selected from the groups included in the definition above; preferably no more than two of the substituents are other than hydrogen.

Certain compounds of the invention may exist in different stereoisomeric forms (e.g., enantiomers, diastereoisomers and atropisomers). The invention contemplates all such stereoisomers both in pure form and in mixture, including racemic mixtures.

Certain compounds will be acidic in nature, e.g. those compounds which possess a phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, calcium, aluminum, gold and silver salts.

Certain basic compounds also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, pyrido-nitrogen atoms may form salts with strong acid, while compounds having basic functionality such as amino groups also form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic

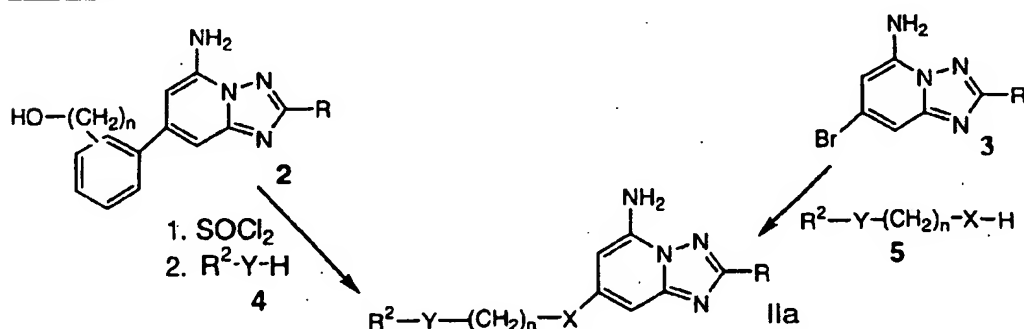
acids well known to those skilled in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH,
 5 potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention.

All such acid and base salts are intended to be pharmaceutically acceptable
 10 salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of formula I are prepared by general methods known in the art. Preferably, the compounds of formula I are prepared by the methods shown in the
 15 following reaction schemes. In the Schemes and examples that follow, the following abbreviations are used : Ph is phenyl, Me is methyl, Et is ethyl, TFA is trifluoroacetic acid, BSA is N,O-bis(trimethylsilyl)acetamide, DMF is dimethylformamide, EtOAc is ethyl acetate, THF is tetrahydrofuran, and DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene.

Compounds of formula IIa where A is C(R¹) can be prepared by methods
 20 described in application WO 01/11799. In addition, compounds wherein Y is not a bond can be prepared by methods illustrated in Scheme 1.

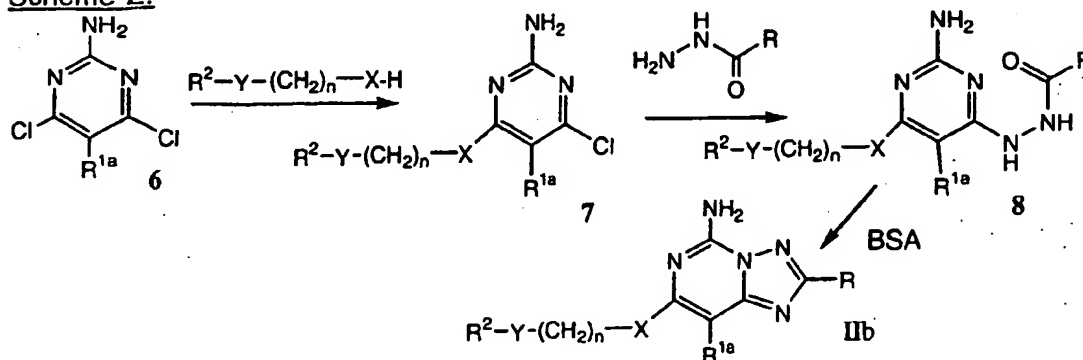
Scheme 1:



Where X is arylene, an intermediate of type 2 may be activated, e.g. to a
 25 chloride, which may then be reacted with a nucleophile 4 (e.g., Y=piperazinyl) to provide IIa. Alternatively, bromide 3 may be reacted with a nucleophile of type 5 provide IIa.

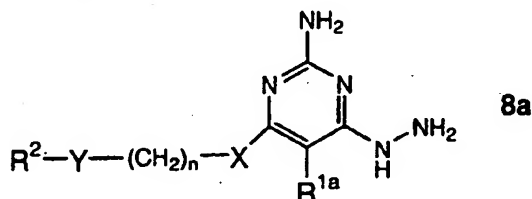
Compounds of formula IIb where A is N, and X is -O-, -S-, or -N(R⁹)- can be prepared by methods described in Schemes 2 and 3.

Scheme 2:



- 5 Chloride 6 is treated with an amine, alcohol or thiol in the presence of base to yield 7. Reaction with the appropriate hydrazide yields 8. Dehydrative cyclization with an agent such as BSA then yields the desired compound of formula IIb.

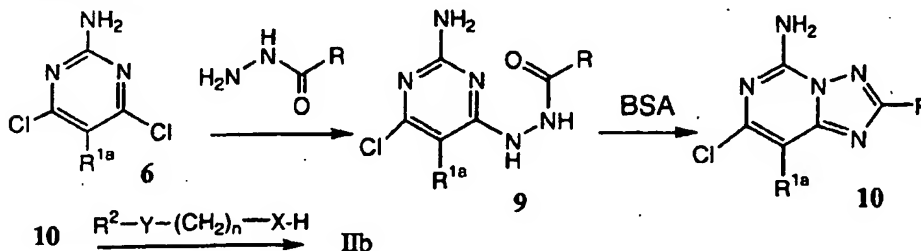
In a variant of this scheme, R in the hydrazide RCONHNH₂ may be a removable protective group such a *t*-butoxy or benzyloxy. In such a case,
 10 deprotection of 8 leads to 8a,



which may be acylated with RCOOH or the corresponding acid chloride, anhydride, or mixed anhydride. This produces a new 8, which may be converted to the desired compound of formula IIb.

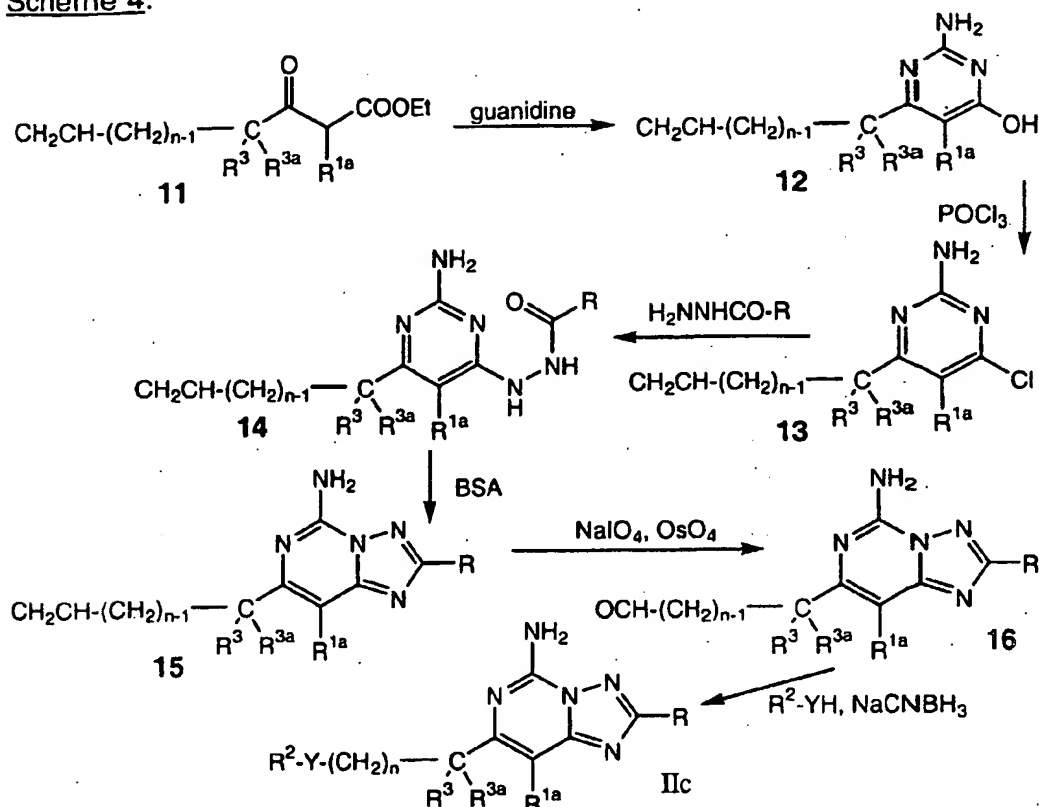
- 15 In Scheme 3, the order of the steps is reversed in order to prepare compounds of formula IIb.

Scheme 3:



In Scheme 4, compounds of formula IIc, wherein A is N and X is $-C(R^3)(R^{3a})-$ are prepared.

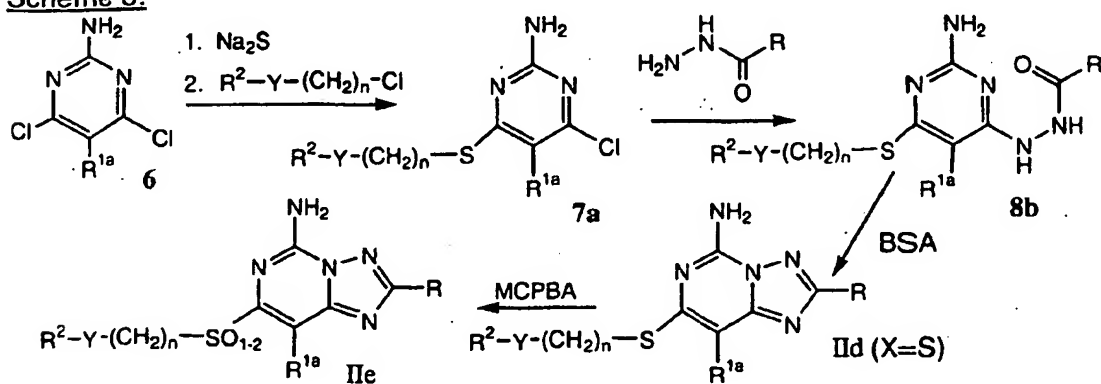
Scheme 4:



- 5 Keto-ester 11 is converted to pyrimidine 12, then to chloride 13. Reaction with a hydrazide provides 14, and BSA cyclization yields 15. The olefinic bond is cleaved to give aldehyde 16. When Y in IIc is linked to the alkylene chain through a nitrogen atom, reductive amination of 16 yields the desired compounds IIc.

- 10 A method of preparing compounds of formula II d or II e where A is N and X is -S-, -SO- or -SO₂- is described in Scheme 5.

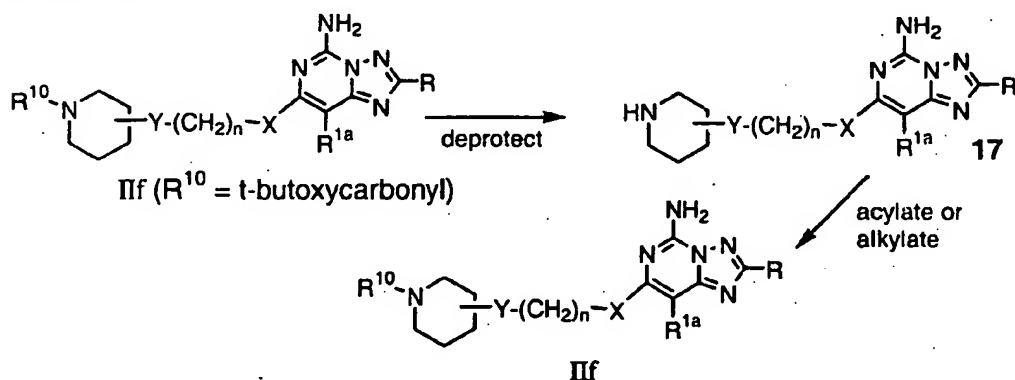
Scheme 5:



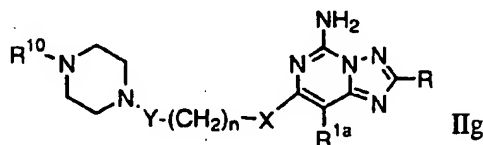
Chloride **6** is reacted with Na_2S and the intermediate then alkylated with a chloride or equivalent to give **7a**. This is then converted to **11d** as in Scheme 2. Subsequent oxidation is employed to prepare the sulfoxide or sulfone of formula **11e**.

For compounds **11f** where R^2 contains an R^{10} moiety, such moieties may be modified, as shown in Scheme 6. When R^{10} is *t*-butoxycarbonyl or benzyloxycarbonyl or the like, the group may be converted to H, e.g. by treatment respectively with acid such as TFA or by hydrogenolysis. The resulting **17** may then be converted to a different compound **11f**. For R^{10} = alkoxycarbonyl or aroyl, acylation may be achieved with an alkyl chloroformate or aroyl chloride or similar acylating agent. For R^{10} = aralkyl, reductive alkylation of **17** may be achieved with an aryl aldehyde and $\text{NaBH}(\text{OAc})_3$.

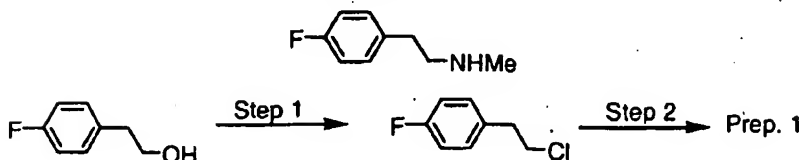
Scheme 6:



Similar methodology can be employed to prepare compounds of formula **11g**:



Preparation 1



20 Step 1: To 2-(4-fluorophenyl)ethanol (2.80 g, 20.0 mmol) add SOCl_2 (7.14 g, 60 mmol). Add two drops DMF and heat at 70 °C for 3 h. Concentrate, partition

between hexane and ice-water, dry (MgSO_4), and concentrate to obtain the chloride as an almost colorless oil.

- Step 2:** Combine the chloride of Step 1 (1.00 g, 6.3 mmol) with 40% aqueous CH_3NH_2 (20 g, 260 mmol). Heat in a sealed tube at 65 °C for 2.5 h. Allow to cool, dilute with water, and extract with EtOAc. Extract the EtOAc with 0.5M HCl, basify with 20% NaOH, and extract with CH_2Cl_2 . Dry (MgSO_4) and concentrate to obtain the title amine as a yellow oil.

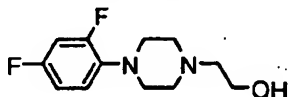
Similarly, convert the corresponding alcohols to the following amines:

(from the analogous bromide)		

- 10 Similarly, convert the corresponding alcohols via the mesylates into the following amines:

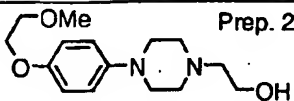
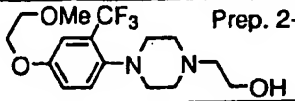
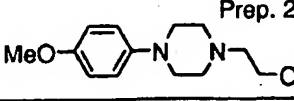
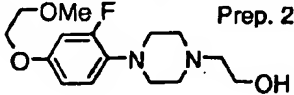
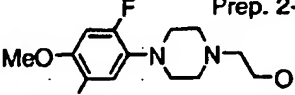
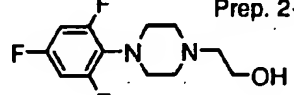
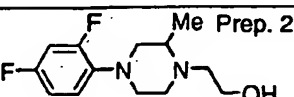
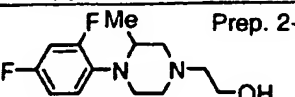
--	--	--

Preparation 2

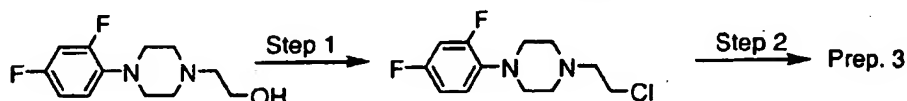
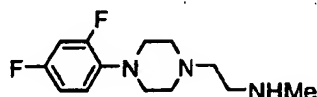


- 15 Combine 1-(2,4-difluorophenyl)piperazine (0.50 g, 2.5 mmol), 2-bromoethanol (0.37 g, 3.0 mmol), and Et_3N (0.30 g, 3.0 mmol) in THF (5 ml). Heat at reflux 4 h, allow to cool, and partition between water and CH_2Cl_2 . Wash the CH_2Cl_2 with brine, dry (MgSO_4), and concentrate to obtain the title alcohol as a yellow oil.

Similarly prepare:

 Prep. 2-2	 Prep. 2-3	 Prep. 2-4
 Prep. 2-5	 Prep. 2-6	 Prep. 2-7
 Prep. 2-8	 Prep. 2-9	

Preparation 3

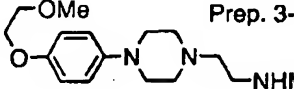
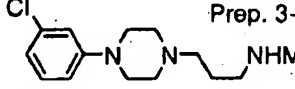
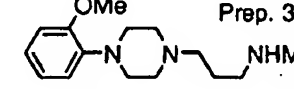
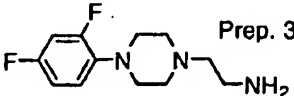
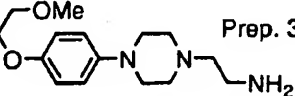
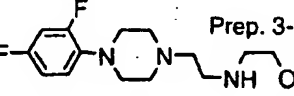
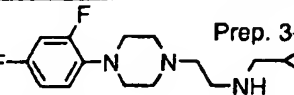
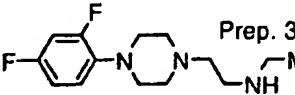
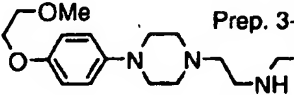
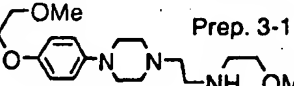
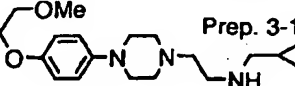
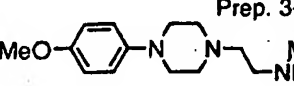


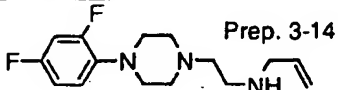
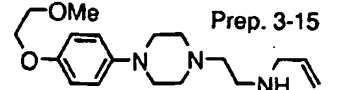
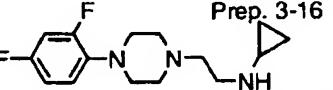
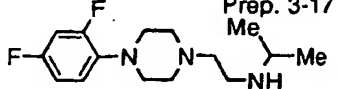
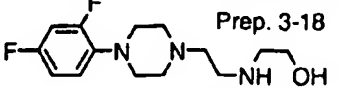
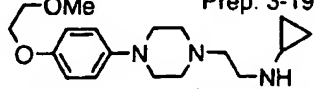
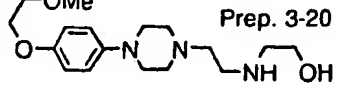
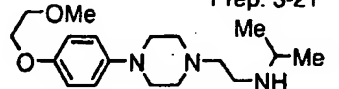
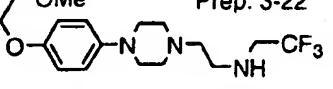
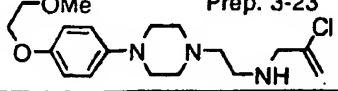
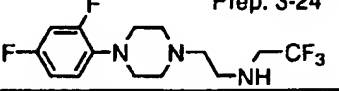
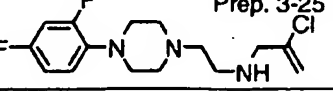
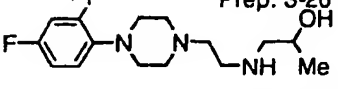
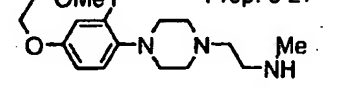
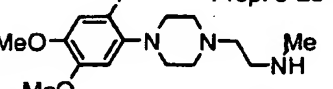
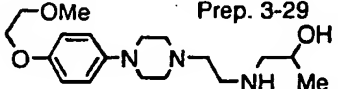
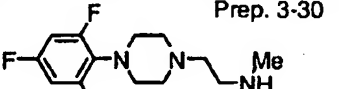
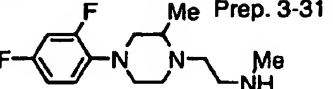
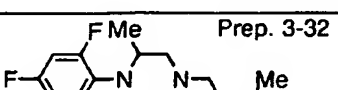
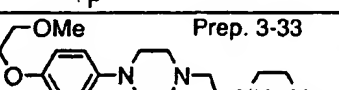
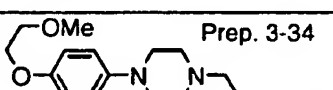
5

Step 1: To the product of Preparation 2 (0.50 g, 2.1 mmol) in CH_2Cl_2 (10 ml) add SOCl_2 (0.49 g, 4.2 mmol). Add two drops DMF and stir 4 h. Concentrate, partition between EtOAc and water, dry (MgSO_4), and concentrate to obtain the chloride as an almost colorless oil.

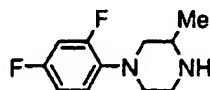
10 Step 2: Combine the product of Step 1 (0.51 g, 2.0 mmol) with 40% aqueous CH_3NH_2 (10 ml, 130 mmol) in EtOH (10 ml). Heat in a sealed tube at 80 °C for 2 h, allow to cool, concentrate, and partition between EtOAc and water. Dry (MgSO_4) and concentrate to obtain the title amine as a yellow oil.

Similarly prepare:

 Prep. 3-2	 Prep. 3-3	 Prep. 3-4
 Prep. 3-5	 Prep. 3-6	 Prep. 3-7
 Prep. 3-8	 Prep. 3-9	 Prep. 3-10
 Prep. 3-11	 Prep. 3-12	 Prep. 3-13

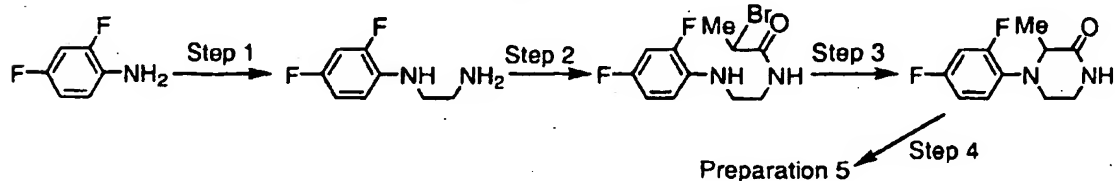
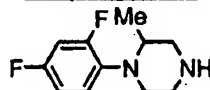
 Prep. 3-14	 Prep. 3-15	 Prep. 3-16
 Prep. 3-17	 Prep. 3-18	 Prep. 3-19
 Prep. 3-20	 Prep. 3-21	 Prep. 3-22
 Prep. 3-23	 Prep. 3-24	 Prep. 3-25
 Prep. 3-26	 Prep. 3-27	 Prep. 3-28
 Prep. 3-29	 Prep. 3-30	 Prep. 3-31
 Prep. 3-32	 Prep. 3-33	 Prep. 3-34

Preparation 4



Combine 2, 4-difluorobromobenzene (4.0g, 20.7mmol), 2-methylpiperazine (24.9g, 249mmol), NaO-*t*Bu (2.79g, 29.0mmol), \pm -BINAP (0.77g, 1.2mmol), and Pd₂(dba)₃ (0.24g, 0.41mmol) in toluene (40ml). Heat at reflux 16h, allow to cool, and extract with 1N HCl (4x50ml). Basify with NaOH to pH 13 and extract with CH₂Cl₂. Dry (MgSO₄) and concentrate to give the product as a brown oil.

Preparation 5



Step 1: Combine 2,4-difluoroaniline (10.0g, 77.4mmol) and 2-bromoethylamine•HBr (15.9g, 77.4mmol) in toluene (100ml). Heat at reflux 16h, allow to cool, and remove the toluene layer. Dissolve the oily layer in water, basify with NaOH to pH 11, and extract with CH₂Cl₂. Dry (MgSO₄), concentrate, and distill at 120-30 °C (1mm).

5 Chromatograph on silica to obtain the product as a brown oil.

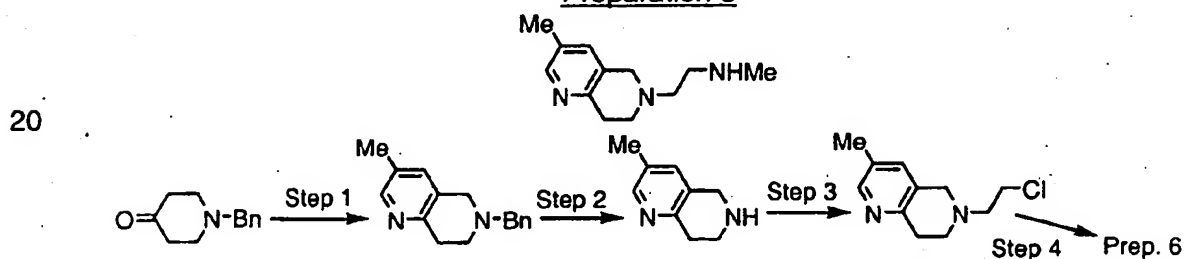
Step 2: Dissolve the product of Step 1 (3.0g, 17mmol) in CH₂Cl₂ (25ml). Cool in ice and add Et₃N (5.3ml, 38mmol), followed by 2-bromopropionyl bromide (2.1ml, 19mmol). Allow to warm to RT, stir 16h, cool in ice, and add more bromide (1.1g) and Et₃N (1.0g). Allow to warm to RT, stir 2h, wash with water, dry (MgSO₄) and

10 concentrate to obtain crude brown oil.

Step 3: Treat the product of Step 2 (5.86g, 19mmol) with DIPEA (2.97g, 23mmol) and KI (1.58g, 9.5mmol) in DMF (15ml). Heat at 80 °C 18h, allow to cool, concentrate and chromatograph on silica to obtain the product as a brown solid.

Step 4: Dissolve the product of Step 3 (1.33g, 5.86mmol) in THF (20ml) and cool in ice. Add slowly 1.0M BH₃•THF solution (15ml, 15mmol). Allow to warm to RT, stir 1h, add additional BH₃•THF solution (7ml), and stir 2h. Cool in ice and quench slowly with MeOH. Concentrate and partition with CH₂Cl₂ and 0.5N NaOH. Dry (MgSO₄), concentrate and purify by PLC to obtain the title compound as a yellow oil.

Preparation 6



Step 1: Combine N-benzyl-4-piperidone (3.57ml, 20mmol), 3-ethoxymethacrolein (3.76ml, 30mmol), NH₄OAc (0.82g, 11mmol), and 28% aqueous ammonia (4.17ml, 62mmol). Heat in a sealed tube at 90 °C 48h, allow to cool, and partition between Et₂O and 1N NaHCO₃. Extract the Et₂O with 1N HCl and basify the extract with NaOH to pH 13. Extract with Et₂O, dry (MgSO₄) and concentrate. Subject the oil to Kugelrohr distillation at 0.5mm, collecting 90-160 °C to obtain the product as an orange oil.

Step 2: Dissolve the product of Step 1 (1.73g, 7.3mmol) in 10:1 MeOH/conc. HCl (44ml). Add 10% Pd/C (0.40g) and hydrogenate at 60psi for 18h. Filter through Celite and concentrate to solid. Dissolve in 95% EtOH and add NaO-tBu (0.70g).

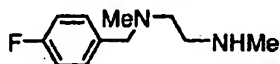
30

Concentrate, treat with EtOH, filter, and concentrate to leave the crude product as a yellow solid.

5 Step 3: Combine the product of Step 2 (0.200g, 1.35mmol), 1-bromo-2-chloroethane (0.45ml, 5.4mmol), and DIPEA (0.28ml, 1.6mmol) in DMF (10ml). Stir 48h, add 1N NaOH (5ml), and extract with Et₂O. Dry (MgSO₄), concentrate and purify by PLC to obtain the product as a yellow oil.

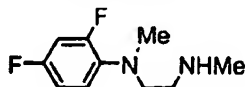
Step 4: Combine the product of Step 3 (0.22g, 1.0mmol), with 40% aqueous MeNH₂ (5.0ml) and EtOH (5ml). Heat in a sealed tube at 100 °C 3h, allow to cool, add 1N NaOH (3ml), concentrate and partition between CH₂Cl₂ and water. Dry (MgSO₄), and
10 concentrate to obtain the title compound as a light brown oil.

Preparation 7



Combine 4-fluorobenzyl chloride (1.74g, 12.0mmol), N,N'-dimethylethylenediamine (3.17g, 36mmol), KI (0.20g, 1.2mmol), and NaHCO₃ (1.51g, 18mmol) in EtOH
15 (20ml). Heat at reflux 4h, filter, and concentrate. Partition with 1N HCl and EtOAc and basify the aqueous layer with NaOH. Extract with CH₂Cl₂, dry (MgSO₄), and concentrate. Distill at 0.5mm up to 100 °C to obtain the title compound as a colorless liquid.

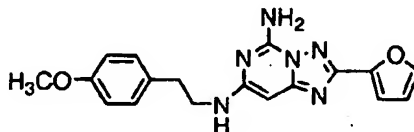
Preparation 8

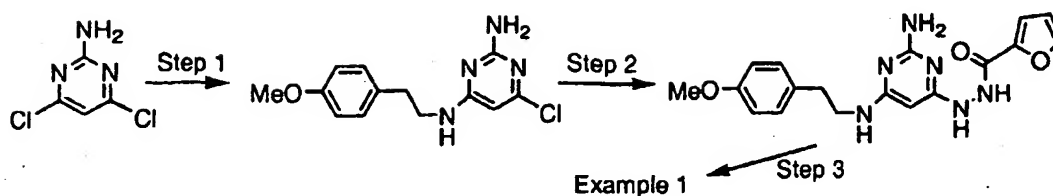


20

Combine 2,4-difluorofluoro-N-methylaniline (1.00g, 6.98mmol) and 4M HCl/dioxane (10ml) in MeOH (10ml). Concentrate to a white solid. Add 3-methyl-2-oxazolidinone (0.60g, 6.98mmol). Heat at 160 °C 18h. Allow to cool, basify with NaOH, and extract with CH₂Cl₂. Dry (MgSO₄), concentrate, and chromatograph on
25 silica to obtain the title compound as a yellow oil. This contains some of the product with aniline methyl removed.

Example 1



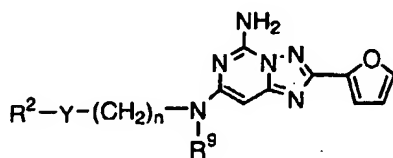


Step 1: Combine 2-amino-4,6-dichloropyrimidine (0.50 g, 3.0 mmol), 2-(4-methoxyphenyl)ethylamine (0.51 g, 3.4 mmol) and K_2CO_3 (0.46 g, 3.4 mmole) in EtOH (8 ml). Heat in a sealed tube at 90 °C 1 h. Stir another 16 h, dilute with water (15 ml), filter, and purify on PLC to obtain the chloropyrimidine as a white solid.

Step 2: Combine the product of Step 1 (0.30 g, 1.08 mmol), 2-furoic hydrazide (0.16 g, 1.3 mmol), and 1.0N HCl (0.4 ml) in EtOH (3 ml). Heat in a sealed tube at 90 °C for 16 h. Basify with NH_3 , extract with EtOAc, and purify on PLC to obtain the hydrazide as a yellow solid.

Step 3: Add the product of Step 2 to BSA (4.0 ml). Heat at 120 °C 18 h. Pour into CH_3OH , concentrate, and purify on PLC to obtain the title compound as a white solid, MS: m/e 351 ($M+1$).

In a similar manner, prepare the following compounds (Et_3N employed as base in Step 1):

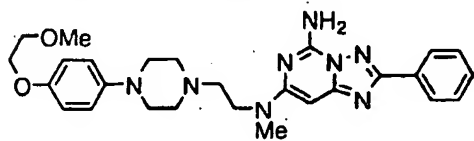


wherein $R^2-Y-(CH_2)_n-N(R^9)-$ is as defined in the table:

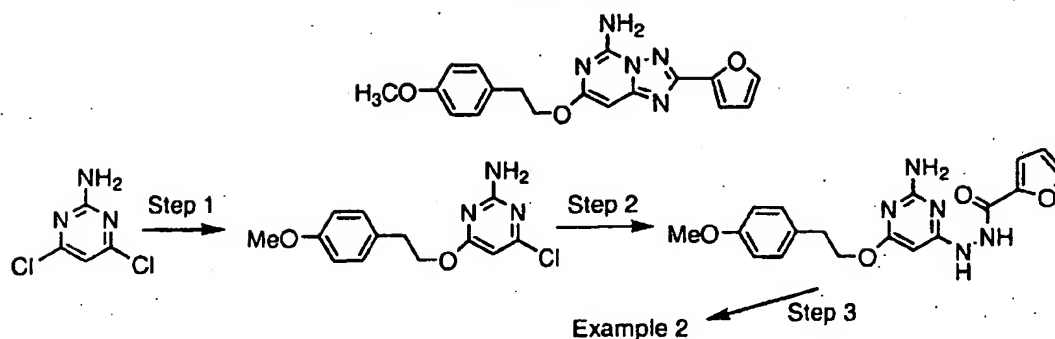
Example	$R^2-Y-(CH_2)_n-N(R^9)-$	MS m/e
1-2		365
1-3		455
1-4		411
1-5		353

1-6		367
1-7		369
1-8		397
1-9		379
1-10		467, 469
1-11		463
1-12		441
1-13		479
1-14		561

Similarly, by employing benzoic hydrazide in place of furoic hydrazide, prepare Example 1-15 as a yellow solid.



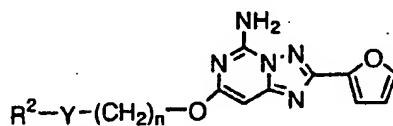
1-15: MS: m/e 503 (M+1)

Example 2

Step 1: To NaH (60% in oil, 0.16 g, 4.0 mmol) in THF (6 ml) add 2-(4-methoxyphenyl)ethanol (0.46 g, 3.0 mmol). Stir 0.5 h and add 2-amino-4,6-dichloropyrimidine (0.50 g, 3.0 mmol). Heat at reflux 24 h. Filter, wash with CH_2Cl_2 , concentrate, and purify on PLC to obtain the chloropyrimidine as a white solid.

Conduct Steps 2 and 3 as in Example 1 to obtain the title compound as a white solid, MS: m/e 352 ($\text{M}+1$).

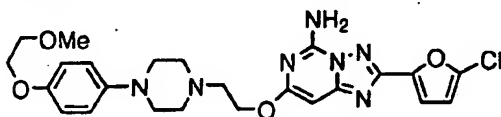
In a similar manner prepare the following:



wherein $\text{R}^2\text{-Y-(CH}_2)_n\text{-O-}$ is as defined in the table:

Example	$\text{R}^2\text{-Y-(CH}_2)_n\text{-O-}$	MS m/e
2-2		366
2-3		442
2-4		398
2-5		480
2-6		548

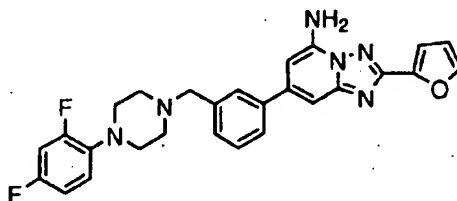
Similarly, by employing 5-chloro-2-furoic hydrazide in place of furoic hydrazide, prepare Example 2-7 as a yellow solid:



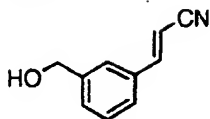
2-7: MS m/e 514, 516 (M+1)

5

Example 3

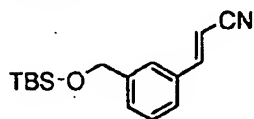


Step 1:



Combine 3-iodobenzyl alcohol (2.00 g, 8.5 mmol), acrylonitrile (0.67 ml, 10.2 mmol), and Et₃N (4.3 ml, 26 mmol) in DMF (30 ml). Purge with N₂ and add (Ph₃P)₂PdCl₂ (0.12 g, 0.17 mmol). Heat in a sealed vessel 3 days at 120°, allow to cool, and partition between CH₂Cl₂ and sat. NaHCO₃. Dry (MgSO₄) and concentrate. Chromatograph on silica to obtain the nitrile as a yellow oil.

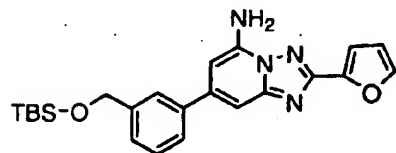
Step 2:



15

Combine the product of Step 1 (1.25 g, 7.9 mmol), *t*-butyldimethylsilyl chloride (1.42 g, 9.4 mmol), and imidazole (0.69 g, 10.2 mmol) in DMF (15 ml). Stir 7h, partition between Et₂O and water, dry the Et₂O (MgSO₄) and concentrate to obtain the silyl ether as a colorless oil.

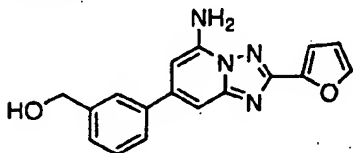
20 Step 3:



To a boiling suspension of potassium t-butoxide (2.34 g, 24.4 mmol) in THF (20 ml) add dropwise over 5h a solution of the product of Step 2 (2.15 g, 7.9 mmol) and 3-(2-furyl)-5-phenylsulfonylmethyl[1,2,4]triazole (2.27g, 7.9mmol) in THF (20 ml). Heat 18h, allow to cool, add water (30 ml), and extract 3x with 5% CH₃OH/CH₂Cl₂.

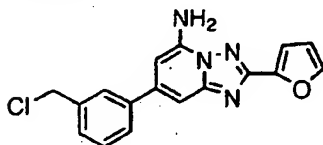
- 5 Dry (MgSO₄), concentrate, and chromatograph on silica to obtain the bicyclic as a yellow solid.

Step 4:



- 10 To the product of Step 3 (0.75 g, 1.8 mmol) in THF (5 ml) add tetrabutylammonium fluoride (1.0M in THF, 2.14 ml). Stir 2h, concentrate, and purify on PLC to obtain the alcohol as a yellow solid.

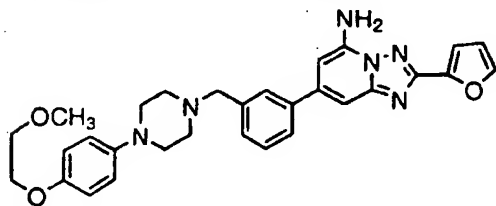
Step 5:



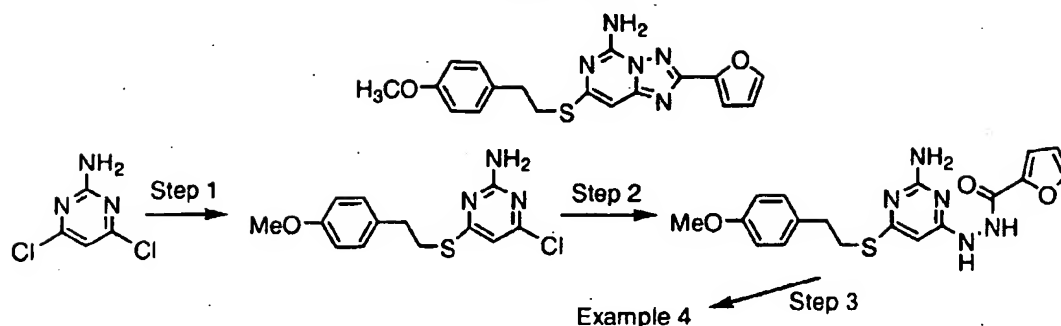
- 15 To the product of Step 4 (0.200 g, 0.65 mmol) in CH₂Cl₂ (10 ml) add SOCl₂ (0.19 ml, 2.6 mmol) and two drops pyridine. Heat at reflux 1h, allow to cool, wash with 1N NaOH, concentrate, dry (MgSO₄), and concentrate to obtain the crude chloride as a yellow solid.

- 20 Step 6: Combine the product of Step 5 (0.090 g, 0.28 mmol) with 1-(2,4-difluorophenyl)piperazine (0.065 g, 0.33 mmol) and diisopropylethylamine (0.058 ml) in DMF (4 ml). Stir 3 days, heat to 60° for 3h, allow to cool, concentrate, and purify on PLC to obtain the title compound as a white solid: MS m/e = 487 (M+1).

In similar fashion, employ 1-(4-(2-methoxyethoxy)phenyl)piperazine to obtain Example 3-2 as a white solid.



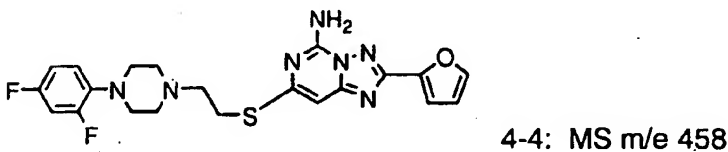
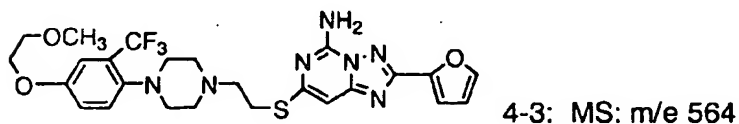
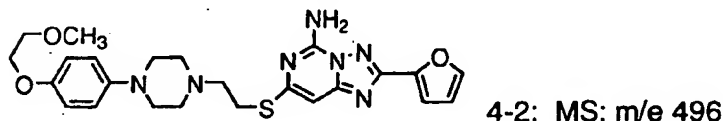
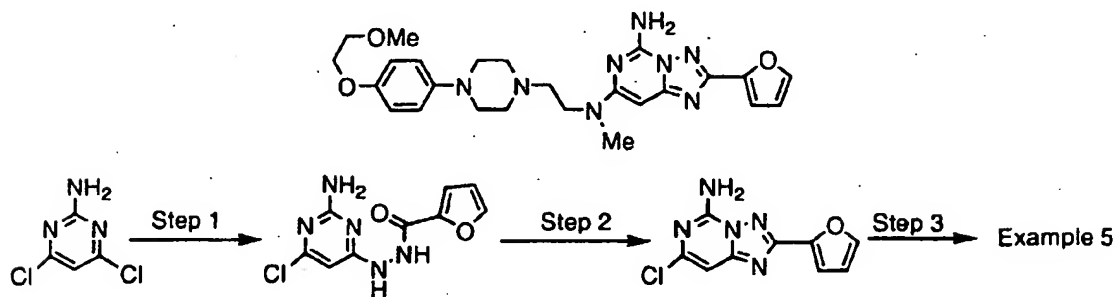
3-2: MS m/e 525

Example 4

Step 1: Combine 2-amino-4,6-dichloropyrimidine (0.50 g, 3.0 mmol) and Na_2S (0.29 g, 3.7 mmole) in DMF (6 ml). Stir for 1 h. Add 4-methoxyphenethyl chloride (0.64 g, 3.77 mmol) and heat at 80 °C 18 h. Add water and extract with EtOAc. Purify on PLC to obtain the chloropyrimidine as a white solid.

Steps 2 and 3: Conduct as for Example 1, Steps 2 and 3, to obtain the title compound as a white solid, MS: m/e 368 (M+1).

In a similar manner, from the products of Preparation 3-2, Step 1, and Preparation 3-6, Step 1, prepare the following:

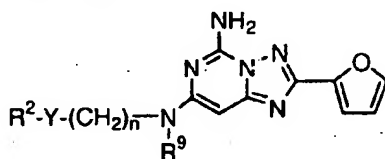
Example 5

Step 1: Combine 2-amino-4,6-dichloropyrimidine (1.00 g, 6.10 mmol), 2-furoic hydrazide (0.97 g, 7.7 mmol) and K_2CO_3 (1.13 g, 8.2 mmole) in EtOH (6 ml). Heat in a sealed tube at 100 °C 18 h. Allow to cool, filter, wash with water to obtain product. Extract the filtrate with EtOAc, concentrate and recrystallize from EtOAc to obtain additional product as a yellow solid.

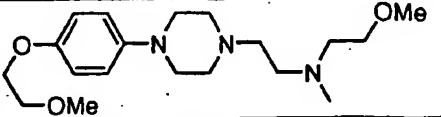
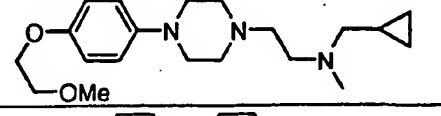
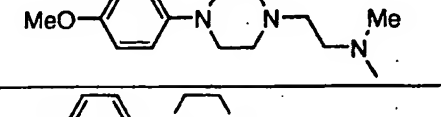
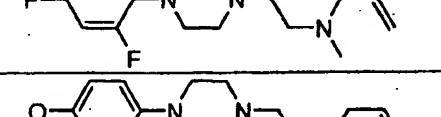
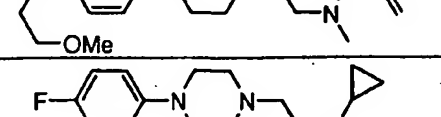
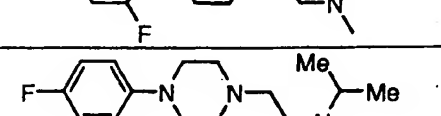
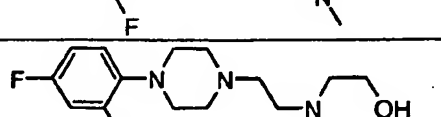
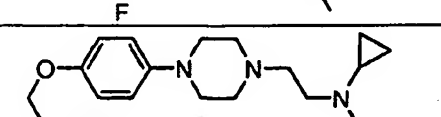
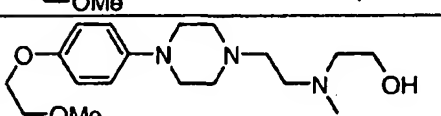
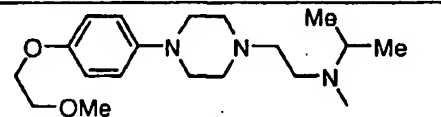
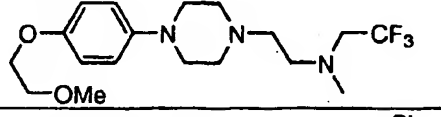
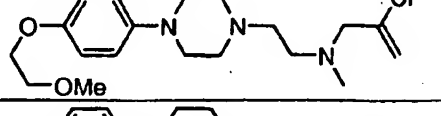
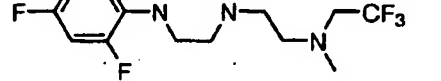

Step 2: Add the product of Step 1 (0.50 g, 2.13 mmol) to BSA (15 ml). Heat at 120 °C 18 h, allow to cool, and pour into CH_3OH (20 ml). Concentrate and heat at reflux in 50% EtOH (40 ml) 1 h. Remove EtOH and extract with CH_2Cl_2 . Dry and concentrate to obtain the product as a white solid.

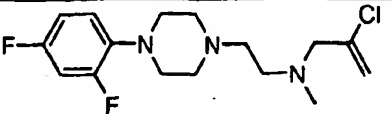
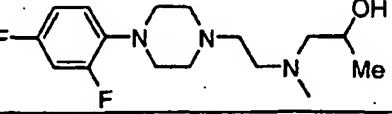
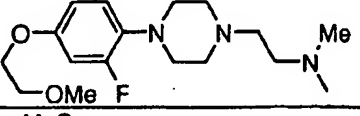
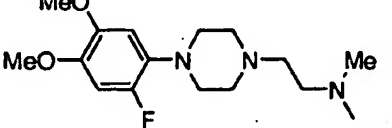
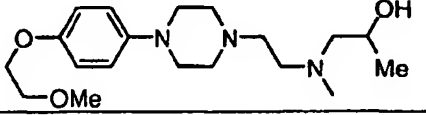
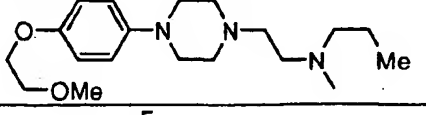
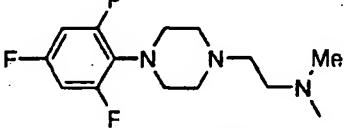
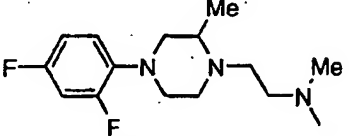
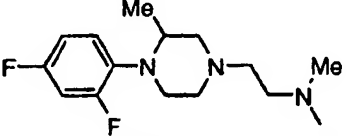
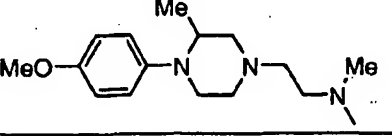
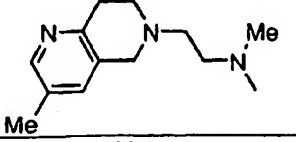
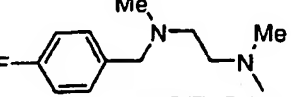
Step 3: Combine the product of Step 2 (0.093 g, 0.39 mmol), the product of Preparation 3-2 (0.127 g, 0.43 mmol), and DBU (0.059 ml, 0.42 mmol) in DMF (2 ml). Heat at 140 °C 2 h, concentrate and purify on PLC to obtain the title compound as a yellow solid, MS: m/e 493 (M+1).

In a similar manner, employing the appropriate amine from Preparation 1 or Preparation 3, prepare the following:



Example	$R^2-Y-(CH_2)_n-N(R^9)-$	MS m/e
5-2		339
5-3		499
5-4		495
5-5		469
5-6		507

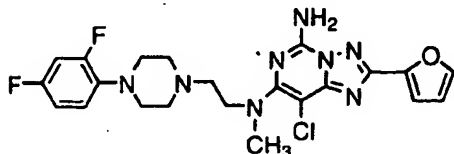
5-7		537
5-8		533
5-9		449
5-10		481
5-11		519
5-12		481
5-13		483
5-14		485
5-15		519
5-16		523
5-17		521
5-18		561
5-19		553, 555
5-20		523

5-21		515, 517
5-22		499
5-23		511
5-24		497
5-25		537
5-26		521
5-27		473
5-28		469
5-29		469
5-30		463
5-31		405
5-32		396

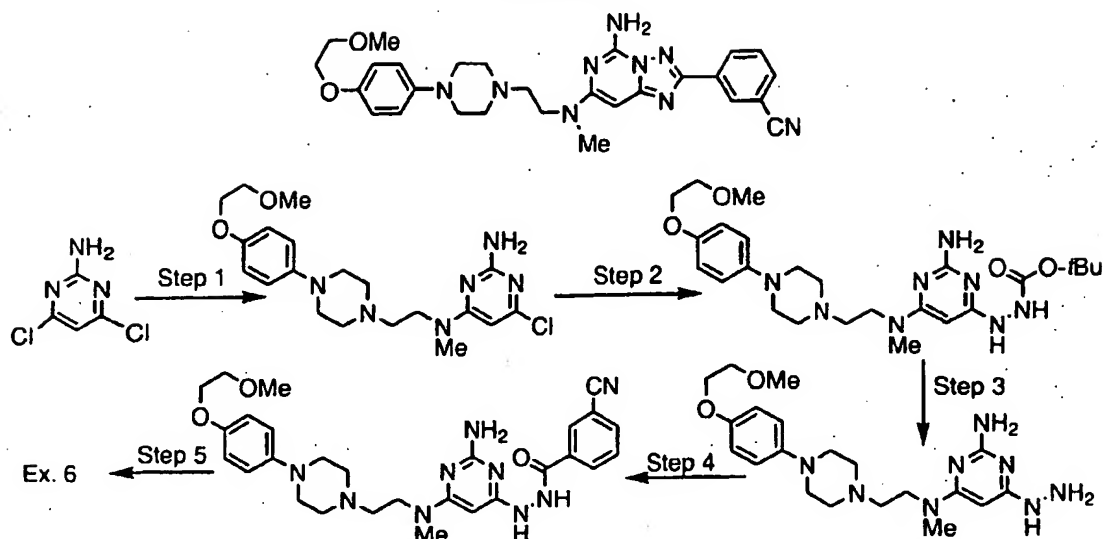
- 27 -

5-33		401, 403
5-34		400
5-35		386
5-36		415, 417
5-37		447, 449
5-38		399, 401
5-39		411
5-40		417
5-41		414
5-42		414
5-43		400

In a similar fashion, employ 2-amino-4,5,6-trichloropyrimidine as starting material to obtain Example 5-44 as a yellow solid.



5-44: MS m/e 489, 491 (M+1)

Example 6

Step 1: Combine 2-amino-4,6-dichloropyrimidine (0.477g, 2.73mmol), the product of Preparation 3-2 (0.800g, 2.73mmol) and DIPEA (0.57ml, 3.27mmole) in DMF (5ml). Heat in a sealed tube at 90 °C 14h. Allow to cool, concentrate, and chromatograph on silica to obtain the product as a yellow solid.

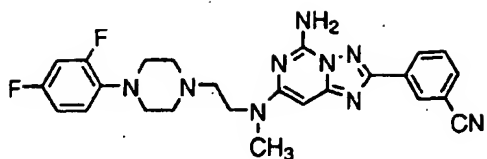
Step 2: Combine the product of Step 1 (1.07g, 2.54mmol), *t*-butyl carbazate (1.01g, 7.61mmol) and 4.0M HCl/dioxane (0.76ml, 3.04mmole) in EtOH (12ml). Heat in a sealed tube at 100 °C 18h, allow to cool, and add 2N NH₃/MeOH (10ml). Concentrate and chromatograph on silica to obtain the product as a yellow solid.

Step 3: Dissolve the product of Step 2 (0.90g, 1.74mmol) in CH₂Cl₂-MeOH (1:17, 20ml). Add 4.0M HCl/dioxane (5.0ml, 20mmole). Stir 18h, concentrate, add 1N NaOH (10ml), and extract with CH₂Cl₂. Dry (MgSO₄), concentrate, and chromatograph on silica to obtain the product as a yellow solid.

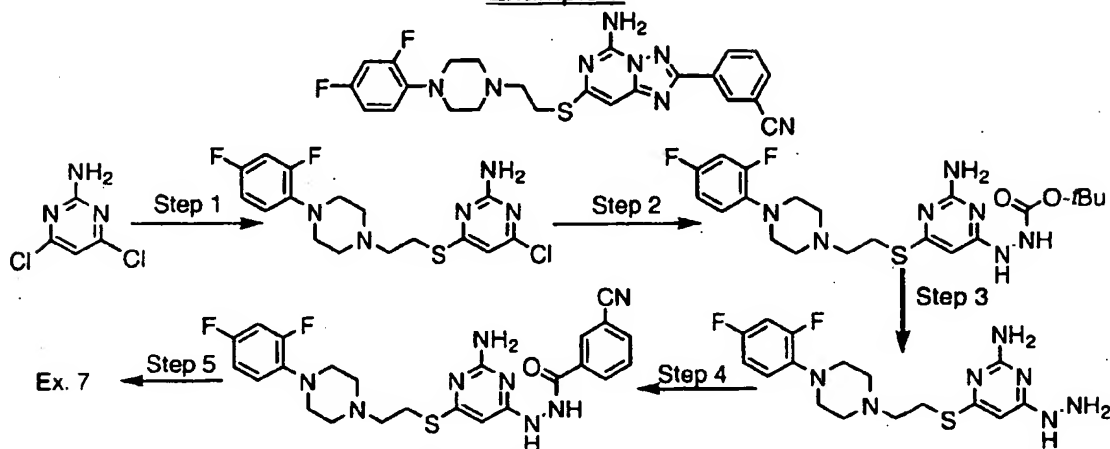
Step 4: To a solution of 3-cyanobenzoic acid (0.047g, 0.32mmol) in DMF (3ml) add the product of Step 3 (0.110g, 0.26mmol), EDCI (0.061g, 0.32mmol), HOBT·H₂O (0.043g, 0.32mmol), and NMM (0.035ml, 0.32mmol). Stir 3h, concentrate, and purify by PLC to obtain the product as a yellow solid.

Step 5: Add the product of Step 4 (0.101g, 0.18mmol) to BSA (6.0ml). Heat at 120 °C 18h, allow to cool, concentrate, add MeOH (20ml), stir 0.5h, concentrate, and purify by PLC to obtain the title compound as a yellow solid, MS: *m/e* 528 (M+1).

In a similar fashion, employ the product of Preparation 3 as starting material to obtain Example 6-2 as a white solid.

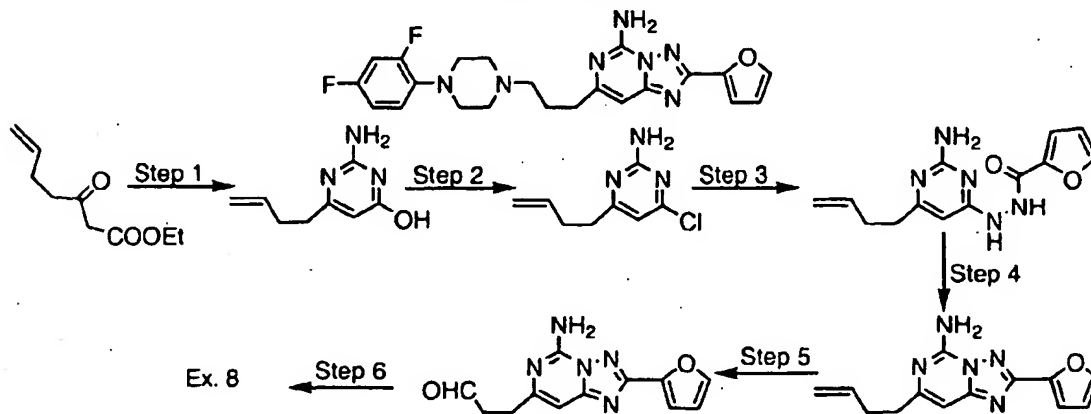


EX. 6-2: MS: m/e 490 (M+1)

Example 7

Step 1: Combine 2-amino-4,6-dichloropyrimidine (0.515g, 3.14mmol) and Na_2S (0.294g, 3.76mmole) in DMF (3ml). Stir for 1h. Add the product of Preparation 3, Step 1 (0.900g, 3.45mmol) in DMF (2ml) and heat at 80 °C 18h. Allow to cool, add CH_2Cl_2 , and filter. Concentrate and chromatograph on silica to obtain the product as a yellow solid.

Steps 2-5: Treat the product of Step 1 according to Example 6, Steps 2-5, to obtain the title compound as an off-white solid, MS: m/e 493 (M+1).

Example 8

Step 1: Combine ethyl 3-oxo-6-heptenoate (6.68g, 39.2mmol) and guanidine carbonate (12.7g, 70.6mmol) in EtOH (100ml). Heat at reflux 20h, allow to cool, and

- 30 -

add CH_2Cl_2 (100ml). Filter, concentrate, and chromatograph on silica to obtain a white solid.

Step 2: Treat the product of Step 1 (2.35g, 14.2mmol) with POCl_3 (20ml). Heat at reflux 2h, concentrate, pour onto ice water, and basify with NaOH to pH9. Extract with CH_2Cl_2 , dry (MgSO_4), concentrate, and chromatograph on silica to obtain a yellow oil.

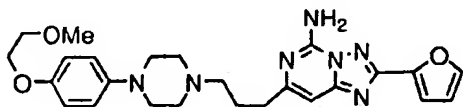
Step 3: Combine the product of Step 2 (0.90g, 4.9mmol), 2-furoic hydrazide (0.865g, 6.86mmol) and 4.0M HCl/dioxane (1.47ml, 5.88mmol) in EtOH (10ml). Heat in a sealed tube at 100 °C 18h, allow to cool, and add 2N NH_3 /MeOH (10ml). Concentrate and chromatograph on silica to obtain the product as a yellow solid.

Step 4: Add the product of Step 3 (0.8g, 2.9mmol) to BSA (10ml). Heat at 130 °C 6h, allow to cool, and concentrate. Wash with water to obtain a yellow solid.

Step 5: Dissolve the product of Step 4 (0.10g, 0.39mmol) in THF (8ml), cool in ice, add water (5ml), then NaIO_4 (0.419g, 1.96mmol). Add two crystals OsO_4 and stir 5h. Partition with CH_2Cl_2 and water, dry (MgSO_4), concentrate, and purify by PLC to obtain a yellow solid.

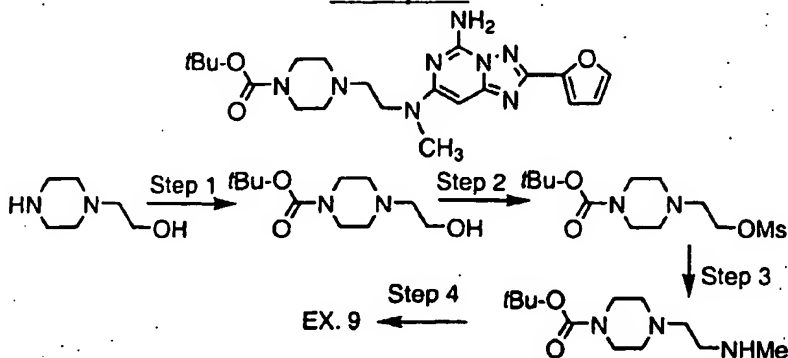
Step 6: Dissolve the product of Step 5 (0.080g, 0.31mmol) in CH_2Cl_2 (5ml). Add 1-(2,4-difluorophenyl)piperazine (0.185g, 0.93mmol), AcOH (0.30ml), and NaCNBH_3 (0.066g, 0.31mmol). Stir 18h, concentrate, and purify by PLC to obtain the title compound as a white solid, MS: m/e = 440 ($\text{M}+1$).

In a similar fashion, employ the appropriate aryl-piperazine to obtain Example 8-2 as a yellow powder.



EX. 8-2: MS: m/e = 478 ($\text{M}+1$)

Example 9



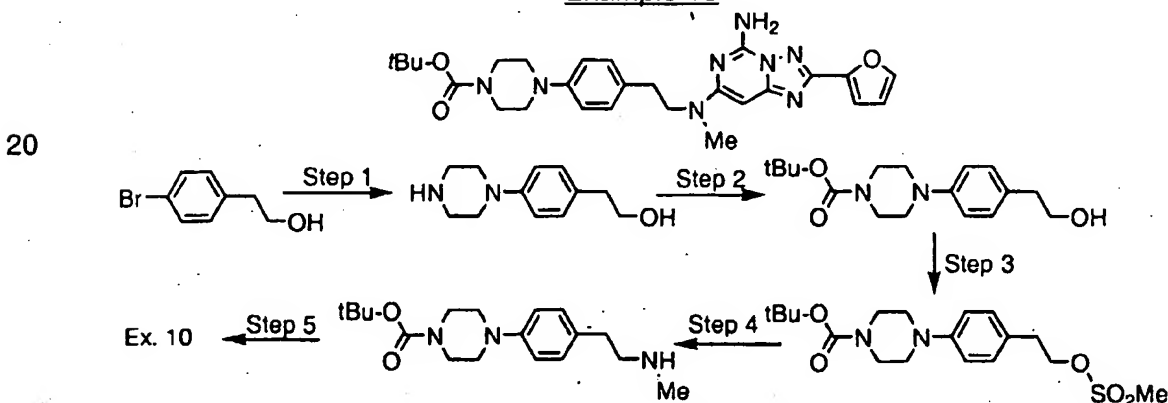
Step 1: Dissolve 1-(2-hydroxyethyl)piperazine (3.25g, 25mmol) in THF (40ml) and cool in ice. Add, portionwise, Boc_2O (5.45g, 25mmol). Allow to warm, stir 3h, concentrate, and treat with hot hexane (50ml). Cool to -15°C and decant the hexane to leave a viscous orange oil.

5 Step 2: Combine the product of Step 1 (3.49g, 15.0mmol) and Et_3N (1.72g, 17.0mmol) in CH_2Cl_2 (40ml) and cool in ice. Add, dropwise, MsCl (1.96g, 17.0mmol) in CH_2Cl_2 (10ml). Allow to warm, stir 0.5h, and concentrate. Partition between Et_2O and water, dry (MgSO_4) and concentrate to give the crude product as viscous oil with solid.

10 Step 3: Combine the crude product of Step 2 (4.6g, ~15mmol) with 40% aqueous MeNH_2 (35g, 0.45mol) and EtOH (35ml). After 1h, concentrate and partition between CH_2Cl_2 and 1N NaOH . Dry (MgSO_4) and concentrate to obtain the crude product as a yellow oil.

15 Step 4: Combine the crude product of Step 3 (0.46g, ~1.5mmol) with the product of Example 5, Step 2 (0.236g, 1.00 mmol), and K_2CO_3 (0.207g, 1.50mmol) in DMF (8ml). Heat in a sealed tube at 130°C 18h, concentrate and partition between EtOAc (10% MeOH) and water. Dry (MgSO_4), concentrate and chromatograph on silica and triturate with Et_2O to obtain the title compound as yellow solid, MS: $m/e = 443$ ($\text{M}+1$).

Example 10



25 Step 1: Combine 2-(4-bromophenyl)ethanol (4.88g, 24.3mmol), piperazine (12.5g, 146mmol), $\text{NaO}-t\text{Bu}$ (3.27g, 34.0mmol), $\pm\text{-BINAP}$ (0.91g, 1.5mmol), and $\text{Pd}_2(\text{dba})_3$ (0.28g, 0.49mmol) in toluene (40ml). Heat at reflux 2h, allow to cool, and extract with 1N HCl (4x50ml). Basify with NaOH to pH 13 and extract with CH_2Cl_2 . Dry (MgSO_4) and concentrate to give a brown oil.

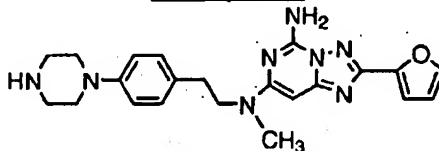
Step 2: Dissolve the product of Step 1 (4.02g, 19.5mmol) in CH_2Cl_2 (50ml). Add Boc_2O (4.51g, 20.5mmol) and then Et_3N (3.26ml, 23.4mmol). Stir 1h and wash with 1N NaOH . Dry (MgSO_4), concentrate and chromatograph on silica to obtain a brown oil.

5 Step 3: Combine the product of Step 2 (1.00g, 3.26mmol) and Et_3N (0.73ml, 5.2mmol) in CH_2Cl_2 (20ml). Cool in ice and add gradually MsCl (0.30ml, 3.9mmol). Stir 1h, wash with sat. NaHCO_3 , dry (MgSO_4) and concentrate to obtain a yellow oil.

Step 4: Dissolve the product of Step 3 (1.15g, 2.99mmol) in EtOH (10ml). Add 40% aqueous MeNH_2 (10ml) and heat in a sealed tube at 100°C 16h, allow to cool, 10 concentrate, and partition between CH_2Cl_2 and 1N NaOH . Dry (MgSO_4), concentrate, and purify by PLC to obtain a yellow oil.

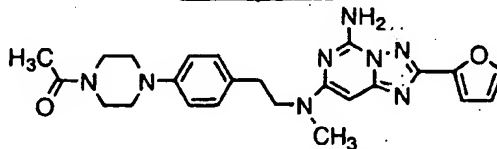
Step 5: Combine the product of Step 4 (0.466g, 1.46mmol), the product of Example 5, Step 2 (0.229g, 0.97 mmol), and K_2CO_3 (0.202g, 1.46mmol) in DMF (8ml). Heat in a sealed tube at 140°C 18h, concentrate and purify on PLC to obtain the title 15 compound as a yellow foam, concentrate, and purify by PLC to obtain the product as a yellow oil MS: $m/e = 519$ ($M+1$).

Example 11

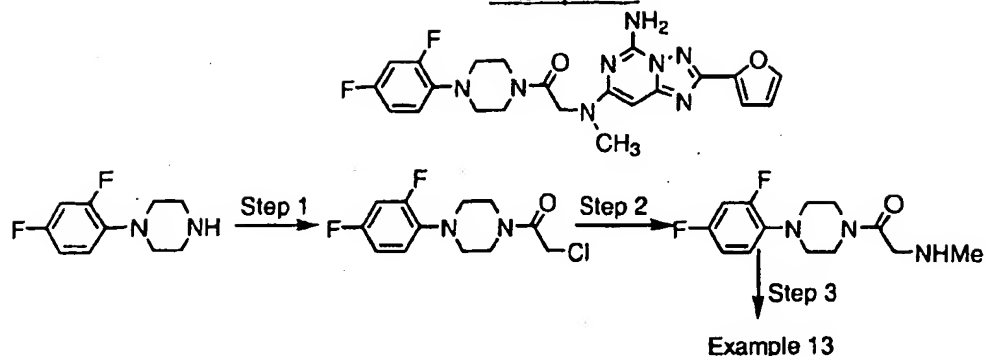


Dissolve the compound of Example 10 (0.215g, 0.41mmol) in 1:1 CH_2Cl_2 - 20 MeOH (10ml) and add 4M HCl /dioxane (2.0ml). Stir 18h and add 7M NH_3/MeOH (4.0ml). Concentrate, and chromatograph on silica to obtain the product as a white foam, MS: $m/e = 419$ ($M+1$).

Example 12



25 Dissolve the compound of Example 11 (0.050g, 0.12mmol) in CH_2Cl_2 (5ml). Add DIPEA (0.031ml, 0.18mmol) and AcCl (0.010ml, 0.14mmol). Stir 1h, concentrate, and purify by PLC to obtain the title compound as a white foam, MS: $m/e = 461$ ($M+1$).

Example 13

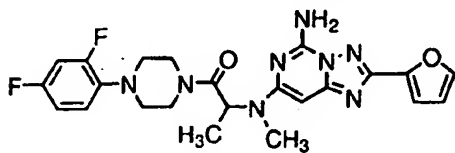
Step 1: Dissolve 1-(2,4-difluorophenyl)piperazine (1.00g, 5.05mmol) in CH_2Cl_2 (5ml).

- 5 Cool in ice and add N-methylmorpholine (0.66ml, 6.05mmol) together with chloroacetyl chloride (0.45ml, 5.6mmol). Stir 2h, concentrate, and partition between EtOAc and water. Dry (MgSO_4) and concentrate to obtain a yellow oil.

- Step 2: Dissolve the product of Step 1 (1.49g, 5.4mmol) in EtOH (10ml). Add 40% aqueous MeNH_2 (15ml) and heat in a sealed tube at 100°C 48h, allow to cool, concentrate, and partition between CH_2Cl_2 and 1N NaOH. Dry (MgSO_4) and
- 10 concentrate to obtain a yellow oil.

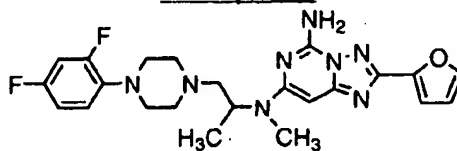
- Step 3: Combine the product of Step 2 (0.137g, 0.51mmol), the product of Example 5, Step 2 (0.080g, 0.34 mmol), and K_2CO_3 (0.070g, 0.51mmol) in DMF (4ml). Heat in a sealed tube at 140°C 18h, concentrate and purify on PLC to obtain the title
- 15 compound as a yellow foam, concentrate, and purify by PLC to obtain the product as a yellow solid MS: $m/e = 469$ ($M+1$).

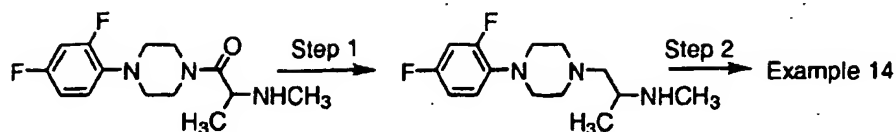
In similar fashion, using 2-bromopropionyl bromide in Step 1, prepare Example 13-2 as an off-white powder.



Ex. 13-2: MS: $m/e = 483$ ($M+1$)

20

Example 14

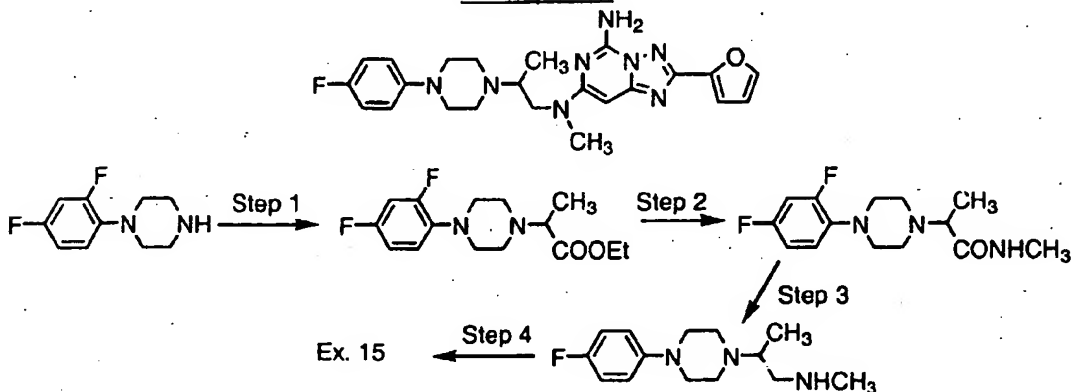


Step 1: Dissolve the product of Example 13-2, Step 2 (0.405g, 1.43mmol) in THF (10ml). Add 1.0M LiAlH₄/Et₂O (0.86ml, 0.86mmol). Heat at 60 °C 4h, allow to cool, add water (0.065ml), then 15% NaOH (0.065ml), then water (3x0.065ml). Filter and concentrate. Partition between CH₂Cl₂ and 1N HCl. Basify the aqueous to pH 12 with NaOH, extract with CH₂Cl₂, dry (MgSO₄) and concentrate. Purify by PLC to obtain a colorless oil.

Step 2: Treat the product of Step 1 with the product of Example 5, Step 2, following the procedure of Example 13, Step 3, to obtain the title compound as a yellow oil;

MS: m/e = 469 (M+1).

Example 15



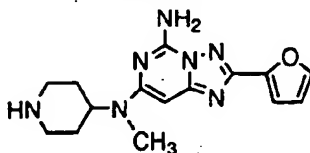
Step 1: Combine 1-(2,4-difluorophenyl)piperazine (1.98g, 10.0mmol), ethyl 2-bromopropionate (1.81g, 10.0mmol), and K₂CO₃ (1.38g, 10.0mmol) in EtOH (15ml). Heat at 80 °C 18h, add more bromide (0.07g), heat another 5h, allow to cool, filter, and concentrate. Partition between Et₂O and water. Dry (MgSO₄) and concentrate to obtain a colorless liquid.

Step 2: Combine the product of Step 1 (2.38g, 8.0mmol) with 40% aqueous MeNH₂ (9.3g, 0.12mol) and EtOH (5ml). Heat in a sealed tube at 80 °C 18h; allow to cool, concentrate, and partition between EtOAc and water. Dry (MgSO₄) and concentrate to obtain a yellow solid. Recrystallization from MeOH-water gives white needles, m.p. 112-3 °C.

Step 3: Treat the product of Step 2 with LiAlH₄ as in Example 14, Step 1 (24h heating) to obtain a yellow oil.

Step 4: Treat the product of Step 3 with the product of Example 5, Step 2, following the procedure of Example 13, Step 3), to obtain the title compound as a colorless oil, MS: $m/e = 451$ ($M+1$).

Example 16

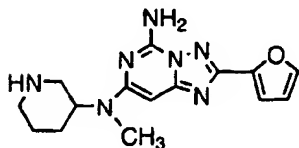


5

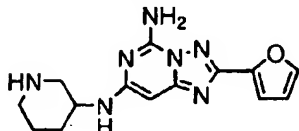
Dissolve the compound of Example 5-41 (0.206g, 0.50mmol) in 1:1 MeOH-CH₂Cl₂ (10ml). Add 4.0M HCl/dioxane (4.0ml). Stir 2h and quench with 2M NH₃/MeOH. Concentrate and chromatograph on silica to obtain the title compound as a yellow oil, MS: m/e 314 ($M+1$).

10

In a similar manner prepare Examples 16-2 and 16-3.

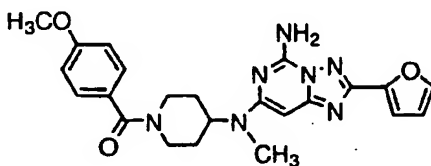


Ex. 16-2: MS: m/e 314 ($M+1$)



Ex. 16-3: MS: m/e 300 ($M+1$)

Example 17

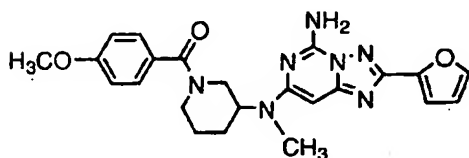


15

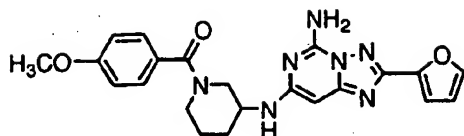
Combine the compound of Example 16 (0.070g, 0.22mmol), 4-methoxybenzoyl chloride (0.058g, 0.34mmol), and DIPEA (0.058g, 0.45mmol) in DMF (4ml). Stir 2h, concentrate, and purify by PLC to obtain the title compound as a yellow solid, MS: m/e 448 ($M+1$).

In similar fashion, convert the respective compounds of Example 16 to Examples 17-2 and 17-3.

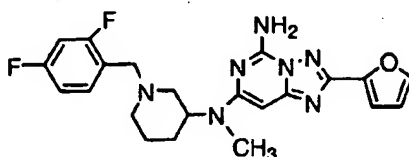
20



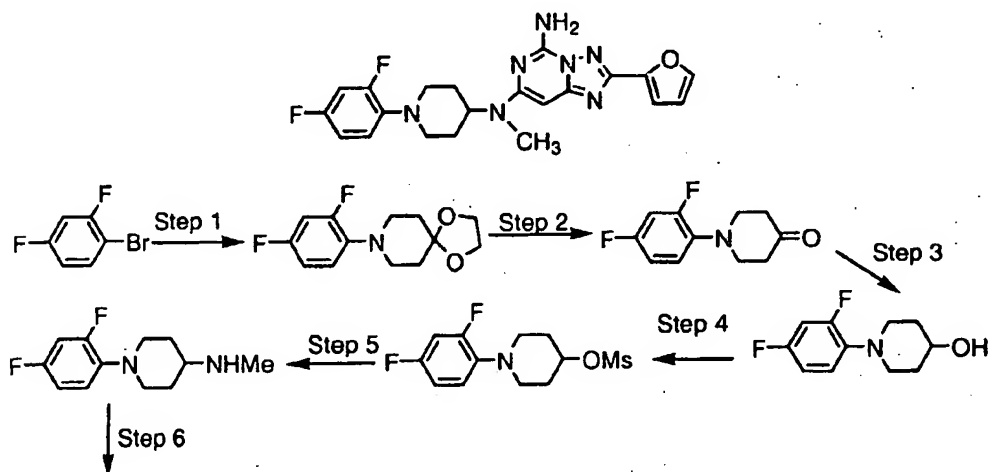
Ex. 17-2: MS: m/e 448 ($M+1$)



Ex. 17-3: MS: m/e 434 (M+1)

Example 18

Combine the compound of Example 17-2 (0.119g, 0.38mmol), 2,4-difluoro-
 5 benzaldehyde (0.054g, 0.38mmol) and NaBH(OAc)₃ (0.157g, 0.74mmol) in CH₂Cl₂
 (10ml). Stir 3h and add more aldehyde (0.016g) and borohydride (0.045g). Stir 18h,
 dilute with CH₂Cl₂, and wash with sat. NaHCO₃, then brine. Dry (MgSO₄) and
 concentrate. Purify on PLC to obtain the title compound as a colorless oil,
 MS: m/e 440 (M+1).

Example 19Ex. 19

Step 1: Combine 2,4-difluorobromobenzene (2.00g, 10.4mmol), 4-piperazinone
 ethylene ketal (2.27g, 15.5mmol), NaO-tBu (1.39g, 14.5mmol), \pm -BINAP (0.387g,
 15 0.65mmol), and Pd₂(dba)₃ (0.119g, 0.21mmol) in toluene (20ml). Heat at reflux 18h,
 allow to cool, and concentrate. Chromatograph on silica to obtain a brown oil.
Step 2: Combine the product of Step 1 (2.55g, 10.0mmol) and 5N HCl (40ml) in THF
 (25ml). Stir 5d and basify with NH₄OH. Concentrate and partition between CH₂Cl₂
 and water. Wash with brine, dry (MgSO₄) and concentrate to obtain a brown oil.

Step 3: Cool the product of Step 2 (1.75g, 8.3mmol) in MeOH (15ml) in ice and add NaBH₄ (0.16g, 4.1mmol). Stir 1h, pour on ice and extract with CH₂Cl₂. Wash with brine, dry (MgSO₄) and concentrate to obtain a yellow oil.

Step 4: Combine the product of Step 3 (1.65g, 7.7mmol) and Et₃N in CH₂Cl₂ (30ml).

- 5 Cool in ice and add methanesulfonyl chloride (1.07g, 9.4mmol). Stir 1h and wash with sat. NaHCO₃. Dry (MgSO₄) and concentrate to obtain a yellow oil.

Step 5: Dissolve the product of Step 4 (1.00g, 3.4mmol) in EtOH (10ml). Add 40% aqueous MeNH₂ (20ml, 0.2mol). Heat in a sealed tube at 100 °C for 3h, allow to cool, and concentrate. Partition between CH₂Cl₂ and water. Wash with brine, dry (MgSO₄)

- 10 and concentrate. Purify on PLC to obtain a yellow oil.

Step 6: Combine the product of Step 5 (0.035g, 0.15mmol) with the product of Example 5, Step 2 (0.041mg, 0.18mmol) and K₂CO₃ (0.031g, 0.23mmol) in DMF (3ml). Heat at 140 °C for 18h. Concentrate and purify by PLC to obtain the title compound as a colorless gum, MS: m/e 426 (M+1).

15

Because of their adenosine A_{2a} receptor antagonist activity, compounds of the present invention are useful in the treatment of depression, cognitive function diseases and neurodegenerative diseases such as Parkinson's disease, senile dementia as in Alzheimer's disease, and psychoses of organic origin. In particular,

20 the compounds of the present invention can improve motor-impairment due to neurodegenerative diseases such as Parkinson's disease.

The other agents known to be useful in the treatment of Parkinson's disease that can be administered in combination with the compounds of formula I include: L-DOPA; dopaminergic agonists such as quinpirole, ropinirole, pramipexole,

25 pergolide and bromocriptine; MAO-B inhibitors such as deprenyl and selegiline; DOPA decarboxylase inhibitors such as carbidopa and benserazide; and COMT inhibitors such as tolcapone and entacapone. One to three other agents can be used in combination with the compounds of formula I, preferably one.

The pharmacological activity of the compounds of the invention was

30 determined by the following *in vitro* and *in vivo* assays to measure A_{2a} receptor activity.

Human Adenosine A_{2a} and A₁ Receptor Competition Binding Assay Protocol

Membrane sources:

A_{2a}: Human A_{2a} Adenosine Receptor membranes, Catalog #RB-HA2a, Receptor Biology, Inc., Beltsville, MD. Dilute to 17 µg/100 µl in membrane dilution buffer (see below).

Assay Buffers:

Membrane dilution buffer: Dulbecco's Phosphate Buffered Saline (Gibco/BRL) + 10 mM MgCl₂.

Compound Dilution Buffer: Dulbecco's Phosphate Buffered Saline (Gibco/BRL) + 10 mM MgCl₂ supplemented with 1.6 mg/ml methyl cellulose and 16% DMSO.

Prepared fresh daily.

Ligands:

A_{2a}: [3H]-SCH 58261, custom synthesis, AmershamPharmacia Biotech, Piscataway, NJ. Stock is prepared at 1 nM in membrane dilution buffer. Final assay concentration is 0.5 nM.

A₁: [3H]- DPCPX, AmershamPharmacia Biotech, Piscataway, NJ. Stock is prepared at 2 nM in membrane dilution buffer. Final assay concentration is 1 nM.

Non-specific Binding:

A_{2a}: To determine non-specific binding, add 100 nM CGS 15923 (RBI, Natick, MA). Working stock is prepared at 400 nM in compound dilution buffer.

A₁: To determine non-specific binding, add 100 µM NECA (RBI, Natick, MA). Working stock is prepared at 400 µM in compound dilution buffer.

Compound Dilution:

Prepare 1 mM stock solutions of compounds in 100% DMSO. Dilute in compound dilution buffer. Test at 10 concentrations ranging from 3 µM to 30 pM. Prepare working solutions at 4X final concentration in compound dilution buffer.

Assay procedure:

Perform assays in deep well 96 well plates. Total assay volume is 200 µl. Add 50 µl compound dilution buffer (total ligand binding) or 50 µl CGS 15923 working solution (A_{2a} non-specific binding) or 50 µl NECA working solution (A₁ non-specific binding) or 50 µl of drug working solution. Add 50 µl ligand stock ([3H]-SCH 58261 for A_{2a}, [3H]- DPCPX for A₁). Add 100 µl of diluted membranes containing the appropriate receptor. Mix. Incubate at room temperature for 90 minutes. Harvest

using a Brandel cell harvester onto Packard GF/B filter plates. Add 45 μ l Microscint 20 (Packard), and count using the Packard TopCount Microscintillation Counter. Determine IC₅₀ values by fitting the displacement curves using an iterative curve fitting program (Excel). Determine Ki values using the Cheng-Prusoff equation.

5 Haloperidol-induced catalepsy in the rat

Male Sprague-Dawley rats (Charles River, Calco, Italy) weighing 175-200 g are used. The cataleptic state is induced by the subcutaneous administration of the dopamine receptor antagonist haloperidol (1 mg/kg, sc), 90 min before testing the animals on the vertical grid test. For this test, the rats are placed on the wire mesh cover of a 25x43 plexiglass cage placed at an angle of about 70 degrees with the bench table. The rat is placed on the grid with all four legs abducted and extended ("frog posture"). The use of such an unnatural posture is essential for the specificity of this test for catalepsy. The time span from placement of the paws until the first complete removal of one paw (*decent latency*) is measured maximally for 120 sec.

15 The selective A_{2A} adenosine antagonists under evaluation are administered orally at doses ranging between 0.3 and 3 mg/kg, 1 and 4 h before scoring the animals.

6-OHDA Lesion of the Middle Forebrain Bundle in Rats

Adult male Sprague-Dawley rats (Charles River, Calco, Como, Italy), weighing 20 275-300 g, are used in all experiments. The rats are housed in groups of 4 per cage, with free access to food and water, under controlled temperature and 12 hour light/dark cycle. The day before the surgery the rats are fasted over night with water *ad libitum*.

Unilateral 6-hydroxydopamine (6-OHDA) lesion of the middle forebrain bundle 25 is performed according to the method described in Ungerstedt et al, *Brian Research*, 24 (1970), p. 485-493, and Ungerstedt, *Eur. J. Pharmacol.*, 5 (1968), p. 107-110, with minor changes. Briefly, the animals are anaesthetized with chloral hydrate (400 mg/kg, ip) and treated with desipramine (10 mpk, ip) 30 min prior to 6-OHDA injection in order to block the uptake of the toxin by the noradrenergic terminals. Then, the animals are placed in a stereotaxic frame. The skin over the skull is reflected and the stereotaxic coordinates (-2.2 posterior from bregma (AP), +1.5 lateral from bregma (ML), 7.8 ventral from dura (DV) are taken, according to the atlas of Pellegrino et al (Pellegrino L.J., Pellegrino A.S. and Cushman A.J., A Stereotaxic Atlas of the Rat 30

Brain, 1979, New York: Plenum Press). A burr hole is then placed in the skull over the lesion site and a needle, attached to a Hamilton syringe, is lowered into the left MFB. Then 8 µg 6-OHDA-HCl is dissolved in 4 µl of saline with 0.05% ascorbic acid as antioxidant, and infused at the constant flow rate of 1 µl /1 min using an infusion pump. The needle is withdrawn after additional 5 min and the surgical wound is closed and the animals left to recover for 2 weeks.

Two weeks after the lesion the rats are administered with L-DOPA (50 mg/kg, ip) plus Benserazide (25 mg/kg, ip) and selected on the basis of the number of full contralateral turns quantified in the 2 h testing period by automated rotameters (*priming test*). Any rat not showing at least 200 complete turns /2h is not included in the study.

Selected rats receive the test drug 3 days after the priming test (maximal dopamine receptor supersensitivity). The new A_{2a} receptor antagonists are administered orally at dose levels ranging between 0.1 and 3 mg/kg at different time points (i.e., 1, 6, 12 h) before the injection of a subthreshold dose of L-DOPA (4 mpk, ip) plus benserazide (4 mpk, ip) and the evaluation of turning behavior.

Using the above test procedures, the following results were obtained for preferred and/or representative compounds of the invention.

Results of the binding assay on compounds of the invention showed A_{2a} Ki values of about 0.3 to about 50 nM, with preferred compounds showing Ki values between 0.3 and 10 nM.

Selectivity is determined by dividing Ki for A1 receptor by Ki for A2a receptor. Compounds of the invention have a selectivity ranging from about 1 to about 1600. Preferred are compounds are those wherein the selectivity is >100.

Preferred compounds showed about a 50-75% decrease in descent latency when tested orally at 1-3 mg/kg for anti-cataleptic activity in rats.

One to three compounds of formula I can be administered in the method of the invention, preferably one.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 70 percent active ingredient. Suitable solid carriers are known in the

art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

5 For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral
10 injection.

Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable
15 carrier, such as an inert compressed gas.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The
20 transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in unit dosage form. In such
25 form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound of formula I in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg to 300 mg, according to the particular application.

30 The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of

the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended dosage regimen for compounds of formula I is oral administration of from 10 mg to 2000 mg/day preferably 10 to 1000 mg/day, in two to four divided doses to provide relief from central nervous system diseases such as Parkinson's disease. The compounds are non-toxic when administered within this dosage range.

The doses and dosage regimen of the other agents used in the treatment of Parkinson's disease will be determined by the attending clinician in view of the approved doses and dosage regimen in the package insert, taking into consideration the age, sex and condition of the patient and the severity of the disease. It is expected that when the combination of a compound of formula I and another anti-Parkinson's disease agent is administered, lower doses of the components will be effective compared to the doses of the components administered as monotherapy. When administered in combination, the compound(s) of formula I and the other agent(s) for treating Parkinson's disease can be administered simultaneously or sequentially. This is particularly useful when the components of the combination are preferably given on different dosing schedules, e.g., one component is administered daily and another every six hours, or when the preferred pharmaceutical compositions are different, e.g. one is preferably a tablet and one is a capsule. A kit comprising the separate dosage forms is therefore advantageous.

The following are examples of pharmaceutical dosage forms which contain a compound of the invention. Those skilled in the art will recognize that dosage forms can be modified to contain both a compound of formula I and a dopaminergic agent. The scope of the invention in its pharmaceutical composition aspect is not to be limited by the examples provided.

Pharmaceutical Dosage Form ExamplesEXAMPLE A-Tablets

No.	Ingredients	mg/tablet	mg/tablet
1.	Active compound	100	500
2.	Lactose USP	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	<u>3</u>	<u>7</u>
Total		300	700

Method of Manufacture

- Mix Item Nos. 1 and 2 in a suitable mixer for 10–15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10–15 minutes. Add Item No. 5 and mix for 1–3 minutes. Compress the mixture to appropriate size and weigh on a suitable tablet machine.

EXAMPLE B-Capsules

No.	Ingredient	mg/capsule	mg/capsule
1.	Active compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade	40	70
4.	Magnesium Stearate NF	<u>7</u>	<u>7</u>
Total		253	700

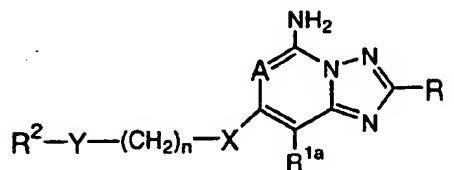
10 Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

- While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

We claim:

1. A compound represented by the structural formula

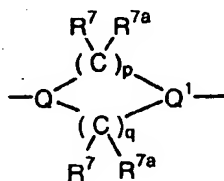


- 5 or a pharmaceutically acceptable salt thereof, wherein:

A is C(R¹) or N;

R¹ and R^{1a} are independently selected from the group consisting of H, (C₁-C₆)-alkyl, halo, CN and -CF₃;

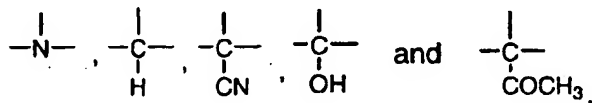
Y is -O-, -S-, -SO₂-, R⁵-heteroaryldiyl, R⁵-arylene or



10

p and q are independently 2-3;

Q and Q' are independently selected from the group consisting of



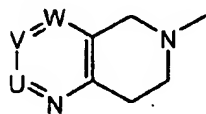
provided that at least one of Q and Q' is -N-;

15

R is R⁵-aryl, R⁵-heteroaryl, R⁶-(C₂-C₆)alkenyl or R⁶-(C₂-C₆)alkynyl;

R² is R⁵-aryl, R⁵-heteroaryl, R⁵-aryl(C₁-C₆)alkyl or R⁵-heteroaryl(C₁-C₆)alkyl;

or R²-Y is



20

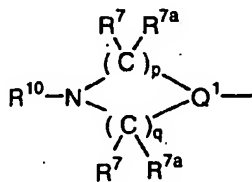
U, V, and W are independently selected from the group consisting of N and CR¹, provided that at least one of U, V and W is CR¹;

n is 1, 2 or 3; and

(a) A is C(R¹) and X is -C(R³)(R^{3a})-, -C(O)-, -O-, -S-, -SO-, -SO₂-, R⁴-arylene, R⁴-heteroaryldiyl, or -N(R⁹)-; or A is C(R¹), Y is a bond, and X is

$-\text{C}(\text{R}^3)(\text{R}^{3a})-$, $-\text{C}(\text{O})-$, $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, R^4 -arylene, $-\text{N}(\text{R}^9)-$ or R^4 -heteroaryldiyl, provided that when X is $-\text{N}(\text{R}^9)-$ or R^4 -heteroaryldiyl, R^2 is not phenyl or phenyl- (C_1-C_6) alkyl; or

(b) A is N, X is $-\text{N}(\text{R}^9)-$, Y is R^5 -arylene and R^2 is



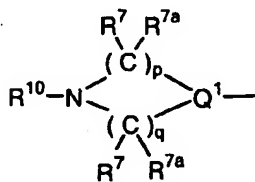
5

or n is 2 or 3; and

(c) A is N and X is $-\text{C}(\text{R}^3)(\text{R}^{3a})-$, $-\text{C}(\text{O})-$, $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{N}(\text{R}^9)-$, R^4 -arylene or R^4 -heteroaryldiyl; or A is N, Y is a bond and X is $-\text{C}(\text{O})-$, $-\text{N}(\text{R}^9)-$, R^4 -arylene or R^4 -heteroaryldiyl; or A is N, Y is $-\text{N}(\text{R}^{9a})-$, $-\text{C}(\text{O})\text{N}(\text{R}^{9a})-$ or

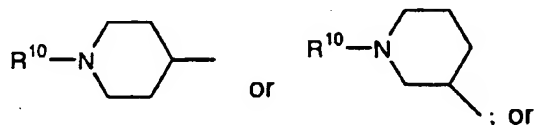
10

$-\text{O}-(\text{CH}_2)_2-\text{N}(\text{R}^{9a})-$, and X is $-\text{N}(\text{R}^9)-$; or A is N, X is $-\text{N}(\text{R}^9)-$, and Y and R^2 together are



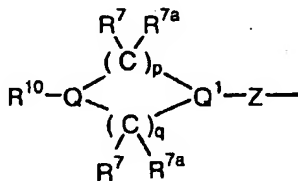
or n is 0; and

(d) A is N, Y is a bond, X is $-\text{N}(\text{R}^9)-$, and R^2 is



15

(e) A is N, X is $-\text{N}(\text{R}^9)-$ and Y and R^2 together are



wherein Z is $-\text{C}(\text{O})-\text{CH}_2-$, $-\text{C}(\text{O})-\text{CH}(\text{C}_1-\text{C}_6 \text{ alkyl})-$, $-\text{CH}_2-\text{CH}(\text{C}_1-\text{C}_6 \text{ alkyl})-$, or $-\text{CH}(\text{C}_1-\text{C}_6 \text{ alkyl})-\text{CH}_2-$;

20

R^3 and R^{3a} are independently selected from the group consisting of H, $-\text{OH}$, C_1-C_6 alkyl, hydroxy (C_1-C_6) alkyl, (C_1-C_6) alkoxy (C_1-C_6) alkyl, amino (C_1-C_6) alkyl, (C_1-C_6) alkylamino (C_1-C_6) alkyl and di (C_1-C_6) alkylamino (C_1-C_6) alkyl;

R^4 is 1-3 substituents selected from the group consisting of H, (C₁-C₆)alkyl, -OH, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo, -CF₃, and -CN;

R^5 is 1-3 substituents independently selected from the group consisting of H, (C₁-C₆)alkyl, -OH, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo, -CF₃, -CN, -NH₂, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl, (C₁-C₆)alkanoylamino, (C₁-C₆)alkanesulfonylamino, (C₁-C₆)alkylthio, (C₁-C₆)alkylthio(C₁-C₆)alkyl, R^6 -(C₂-C₆)alkenyl, R^6 -(C₂-C₆)alkynyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy-C(O)-amino, or heterocycloalkyl(C₁-C₆)alkyl;

R^6 is 1 to 3 substituents independently selected from the group consisting of H, (C₁-C₆)alkyl, -OH, (C₁-C₆)alkoxy and halo;

R^7 and R^{7a} are independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, R^8 -aryl and R^8 -heteroaryl, or an R^7 and an R^{7a} substituent on the same carbon can form =O;

R^8 is 1 to 3 substituents independently selected from H, (C₁-C₆)alkyl, -OH, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo, -CF₃, and -CN;

R^9 and R^{9a} are independently selected from the group consisting of H, (C₁-C₆)alkyl, hydroxy(C₂-C₆)alkyl, (C₁-C₆)alkoxy(C₂-C₆)alkyl, amino(C₂-C₆)alkyl, (C₁-C₆)alkylamino(C₂-C₆)alkyl, di(C₁-C₆)alkylamino(C₂-C₆)alkyl, halo-(C₃-C₆)alkenyl, CF₃-(C₁-C₆)alkyl, (C₃-C₆)alkenyl, -(C₃-C₆)cycloalkyl and (C₃-C₆)cycloalkyl-(C₁-C₆)alkyl; and

R^{10} is H, -C(O)-O-(C₁-C₆)alkyl, R^5 -aryl, -C(O)-(C₁-C₆)alkyl, -C(O)-(R⁵-aryl) or R^5 -aryl-(C₁-C₆)alkyl.

2. The compound of claim 1 wherein A is N.

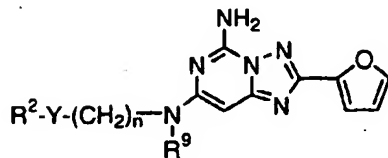
3. The compound of claim 1 wherein X is -O-, -S-, -N(R⁹)- or R⁴-arylene.

4. The compound of claim 1 wherein Y is a bond or piperazinyl.

5. The compound of claim 1 wherein R² is R⁵-aryl.

6. The compound of claim 1 wherein R is furyl.

7. A compound of claim 1 selected from the group consisting of compounds of the formula



wherein $R^2-Y-(CH_2)_n-N(R^9)-$ is as defined in the table:

$R^2-Y-(CH_2)_n-N(R^9)-$

8. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 in a pharmaceutically acceptable carrier.

9. The use of a compound of claim 1 for the preparation of a medicament for treating a central nervous system disease or stroke.
- 5 10. The use of claim 9 for treating depression, cognitive diseases or neurodegenerative diseases.
11. A method of claim 10 for treating Parkinson's disease, senile dementia or psychoses of organic origin.
- 10 12. A pharmaceutical composition comprising a therapeutically effective amount of a combination of a compound of claim 1 and one to three other agents useful in treating Parkinson's disease in a pharmaceutically acceptable carrier
- 15 13. The use of a combination of a compound of claim 1 and one to three other agents useful in treating Parkinson's disease for the preparation of a medicament for treating Parkinson's disease.
- 20 14. A kit comprising in separate containers in a single package pharmaceutical compositions for use in combination to treat Parkinson's disease wherein one container comprises a pharmaceutical composition comprising an effective amount of a compound of formula I in a pharmaceutically acceptable carrier, and wherein, in separate containers, one or more pharmaceutical compositions each comprise an effective amount of an agent useful in the treatment of Parkinson's disease in a
- 25 pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/US 02/37915

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/505 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

PAJ, EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, Y	PATENT ABSTRACTS OF JAPAN vol. 2002, no. 06, 4 June 2002 (2002-06-04) & JP 2002 037787 A (KYOWA HAKKO KOGYO CO LTD), 6 February 2002 (2002-02-06) abstract	1-14
Y	WO 99 43678 A (ICHIMURA MICHIO ; NAKAMURA AKIKO (JP); SHIMADA JUNICHI (JP); SHIOZA) 2 September 1999 (1999-09-02) page 17 -page 22	1-14
Y	EP 1 116 722 A (KYOWA HAKKO KOGYO KK) 18 July 2001 (2001-07-18) claim 1; table 1	1-14
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

S document member of the same patent family

Date of the actual completion of the international search

12 February 2003

Date of mailing of the international search report

28/02/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Baston, E

INTERNATIONAL SEARCH REPORT

Inter application No
PCT/US 02/37915

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 976 753 A (KYOWA HAKKO KOGYO KK) 2 February 2000 (2000-02-02) table 1 ---	1-14
Y	EP 0 666 079 A (KYOWA HAKKO KOGYO KK) 9 August 1995 (1995-08-09) claim 1 ---	1-14
Y	WERMUTH ET AL: "The Practise of Medicinal Chemistry" , PRACTICE OF MEDICINAL CHEMISTRY, XX, XX, PAGE(S) 203-237 XP002190259 page 211 -page 215 -----	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern Application No
PCT/US 02/37915

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 2002037787 A	06-02-2002	NONE	
WO 9943678 A	02-09-1999	AU 2639299 A WO 9943678 A1	15-09-1999 02-09-1999
EP 1116722 A	18-07-2001	AU 5757999 A BR 9914040 A CA 2344828 A1 EP 1116722 A1 HU 0103921 A2 NO 20011417 A CN 1328560 T WO 0017201 A1	10-04-2000 15-01-2002 30-03-2000 18-07-2001 29-04-2002 21-05-2001 26-12-2001 30-03-2000
EP 0976753 A	02-02-2000	AU 743910 B2 AU 6422198 A EP 0976753 A1 US 6222035 B1 WO 9842711 A1	07-02-2002 20-10-1998 02-02-2000 24-04-2001 01-10-1998
EP 0666079 A	09-08-1995	AT 208199 T AU 7237294 A DE 69428977 D1 DE 69428977 T2 EP 0666079 A1 US 5565460 A CA 2144330 A1 ES 2165393 T3 WO 9503806 A1	15-11-2001 28-02-1995 13-12-2001 11-07-2002 09-08-1995 15-10-1996 09-02-1995 16-03-2002 09-02-1995